# 3-O-Demethylation of thebaine and the synthesis of a *flacourtia* aglycone from benzoic acid

*Brennan Murphy*

*Department of Chemistry*

Submitted in partial fulfillment of the requirements for the degree of

*Master of Science*

Faculty of Mathematics and Science, Brock University

St. Catharines, Ontario, Canada

Abstract

Two synthetic projects were embarked upon, both fraught with protecting group nuance and reaction selectivity. Transformations of the opiate skeleton remain a valuable tool for the development of new medicines. Thebaine, a biosynthetic intermediate in the expression of morphine, was converted in three steps to oripavine through two parallel modes. Through the use of protecting group manipulations, two irreversible scaffold rearrangements were avoided during aryl methyl ether bond cleavage. This chemistry constitutes a new path in manipulations of the morphinan scaffold through protective groups.

A new compound family, the flacourtosides, contains an unusual cyclohexenone fragment. The newly described compounds show in preliminary tests antiviral activity against dengue and chikungunya. This aglycone was approached on three pathways, all beginning with the chemoenzymatic dihydroxylation of benzoic acid. A first attempt from a known vinyl epoxide failed to epimerize and cooperate under deprotective conditions. A second and third attempt made use of a diastereoselective dihydroxylation reaction, which was critical in reaching the correct stereochemistry and oxidation state. The methyl ester of the aglycone was prepared, constituting the first synthesis of the non-trivial natural product framework.

Acknowledgments

This work was made possible by the generous support supplied by Dr. Hudlicky and Brock University. Thank you to my examining committee in their kind attention and criticism to this work. Thank you Razvan for your endless patience with me. My laboratory mentors: Dr. David Adams, Dr. Ian Taschner, Dr. John Trant, Dr. Ales Machara, Dr. Ivan Snajdr, Dr. John Hayward, Dr. Sergey Vshyvenko, Dr. Vimal Varghese, Dr. Atkinson, and especially Dr. Mary Ann Endoma Arias, you have all bestowed upon me knowledge both chemically and socially that I may leap out into a larger and better world, thank you.

My laboratory peers: Jordan Froese, Setu Gupta, Jason Hudlicky, Zemane W'Giorgis, Mariia Makarova, Pavlina Horakova, and Chelsea Rintelmann. You have all made positively shaped me through the countless hours in a laboratory and the all-too-infrequent nights at the bar, thank you all for the support through toil and joke upon joke. To my family and their support in my wayward adventures, especially Eda Englund.

LIST OF SCHEMES

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

| | |
|---|---|
| 2,2-DMP | 2,2-Dimethoxypropane |
| 9-BBN | 9-Borabicyclo[3.3.1]nonane |
| AcOH | Acetic acid |
| AZADO | 2-Azaadamantane *N*-Oxyl |
| [Bmim]Cl | Butyl-methyl-imidazolium chloride |
| Bn | Benzyl |
| Bz | Benzoyl |
| CAN | Ceric ammonium nitrate |
| CDI | 1,1'-Carbonyldiimidazole |
| Collidine | 2,4,6-Trimethylpyridine |
| DBI | Dibromoisocyanuric acid |
| DBU | 1,8-Diazabicycloundec-7-ene |
| DCE | 1,2-Dichloroethane |
| DDQ | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAD | Diethyl azodicarboxylate |
| DIBAL | Diisobutylaluminum hydride |
| DIPEA | *N*,*N*-Diisopropylethylamine |
| DMC | Dimethyl carbonate |

| | |
|---|---|
| DMP | Dess-Martin periodinane |
| DMSO | Dimethyl sulfoxide |
| IBX | 2-Iodoxybenzoic acid |
| LHMDS | Lithium bis(trimethylsilyl)amide |
| L-Selectride | Lithium tri-*sec*-butyl(hydrido)borate |
| *m*CPBA | *meta*-Chloroperoxybenzoic acid |
| Me | Methyl |
| MeCN | Acetonitrile |
| MOM | Methoxymethyl |
| Ms | Methanesulfonyl |
| NaHMDS | Sodium bis(trimethylsilyl)amide |
| NBS | *N*-bromo-succinimide |
| NBSH | *o*-Nitrobenzenesulfonyl hydrazide |
| *n*Bu | *n*-Butyl |
| *n*Pr | *n*-Propyl |
| *o*DCB | *o*-Dichlorobenzene |
| Ph | Phenyl |
| PhMe | Toluene |
| PIFA | [Bis(trifluoroacetoxy)iodo]benzene |

| | |
|---|---|
| PivCl | Pivaloyl chloride |
| PMB | *p*-Methoxylbenzyl |
| PMP | *p*-Methoxyphenyl |
| PPTS | Pyridinium *p*-toluenesulfonate |
| TBAF | Tetra-*n*-butylammonium fluoride |
| Tf | Trifluoromethylsulfonyl |
| TFA | Trifluoroacetic acid |
| TIPS | Triisopropylsilyl |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMANO | Trimethylamine *N*-oxide |
| TMEDA | *N,N,N',N'*-Tetramethylethylenediamine |
| TMS | Trimethylsilyl |
| Ts | *p*-Toluenesulfonyl |
| Vitride | Sodium bis(2-methoxyethoxy)aluminum hydride |

1. INTRODUCTION

The production of meaningful quantities of medicines and materials is still in development. The science of chemical synthesis remains a fledgling endeavor. Extending the evolutionary products of nature to the purposeful treatment of the ill is a humanitarian objective and remains a challenging scientific pursuit.

Described herein are two projects: a relay synthesis of oripavine, which serves as an important precursor to pharmaceutical pain-killers and antidotes, and the synthesis of a phenolglycoside aglycone which has shown medicinal value in the treatment of dengue, chikungunya, and malaria, Figure 1.

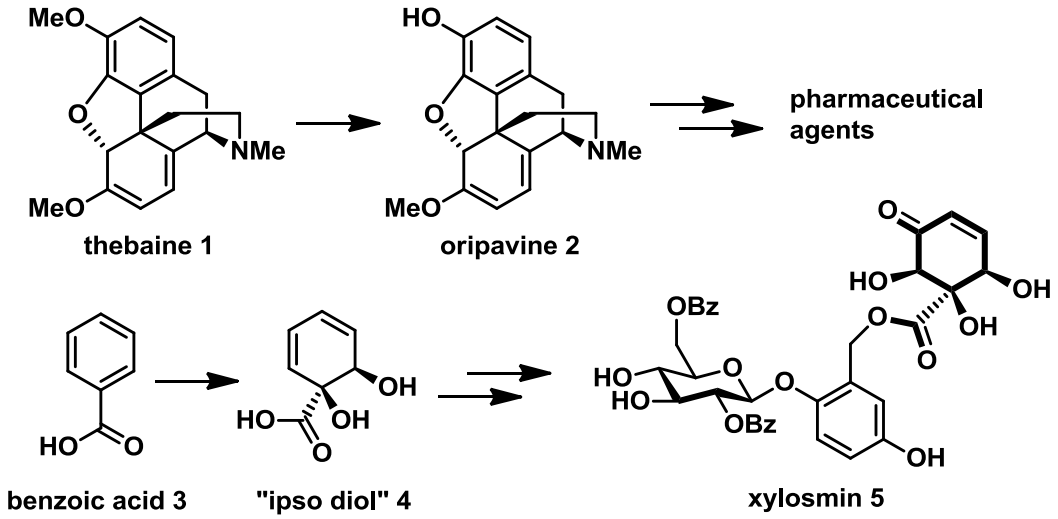



Figure 1. Thesis objectives.

## 2. HISTORICAL

### 2.1 Opiate-derived pharmaceutical agents

The pharmacological effects of opium have been known for millennia, and so has the addictive and lethal risk associated with using opium or its purified components.[1] The anti-nociceptive quality of natural opium alkaloids,[2] Figure 1, and derivatives thereof, Figure 2, continue to have valid medical and scientific applications.

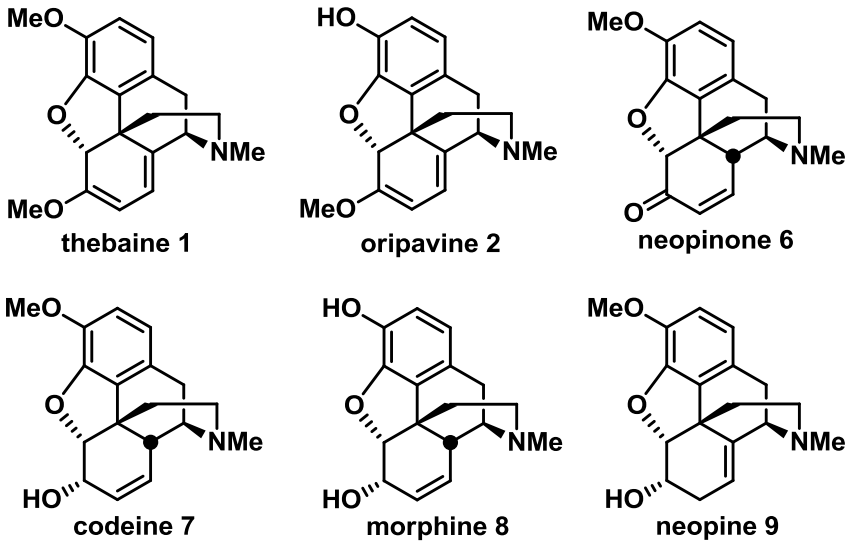



Figure 2. Representative opium alkaloids.

Chemical production of these pharmaceutical agents is dependent on the annual opium poppy's cultivation and alkaloid yield.[3] Because total synthesis of these complex structures is economically prohibitive,[4] harvesting compounds from nature and then chemically modifying them for a set purpose is by far the easiest

route to a final product.[5,6] The final product of interest governs the choice of natural starting material and the synthetic route chosen.

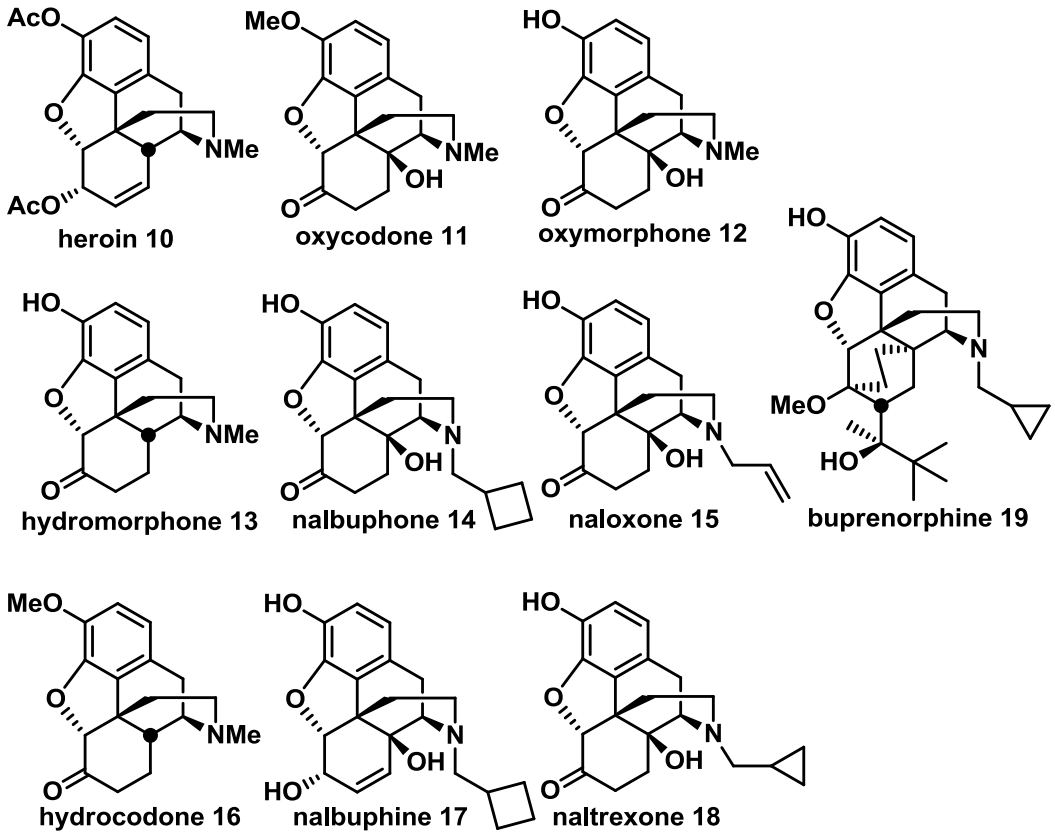



Figure 3. Representative semisynthetic opiate drugs.

Generalization of early transformations followed by late-stage divergence to the desired drug would constitute an ideal state of the art. When processing semisynthetic opiates,[5] late-stage divergence in chemical modification is strictly better from an economical point of view. Acquiring large quantities of this

hypothetical chemical intermediate from natural sources is where thebaine and oripavine have their story.

When referring to the certain anatomy of the morphinan scaffold, a numbering- and ring-lettering system shown below are used, Figure 4. Such a diagram assists in communication between researchers as to the exact subtleties of a particular opiate-derived substance.

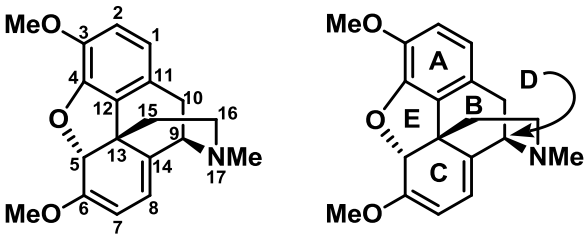



Figure 4. Morphinan numbering system and ring assignment.

The two naturally occurring alkaloids, thebaine **1** and oripavine **2**, are produced through a long sequence within the poppy, Figure 4, and serve as intermediates along the branched biosynthetic pathway to codeine and morphine. Thebaine and oripavine may be intercepted along this biosynthetic pathway and then subjected to chemical synthesis that produces unnatural opiate drugs.[3] These derivatives have substantially different pharmacological profiles: some are potent analgesics or non-addictive pain-killers, and others even serve as therapeutic agents for addiction and/or overdose to other opiates, Figure 3. The

natural alkaloid content of *P. somniferum* (compared to *top1* {**t**hebaine **o**ripavine **p**oppy **1**}) dry straw mass is morphine: 2.4 % (0.05%), codeine 0.1% (0.01%), oripavine 0.03% (0.8%), thebaine 0.1% (2.0%).[7,8]

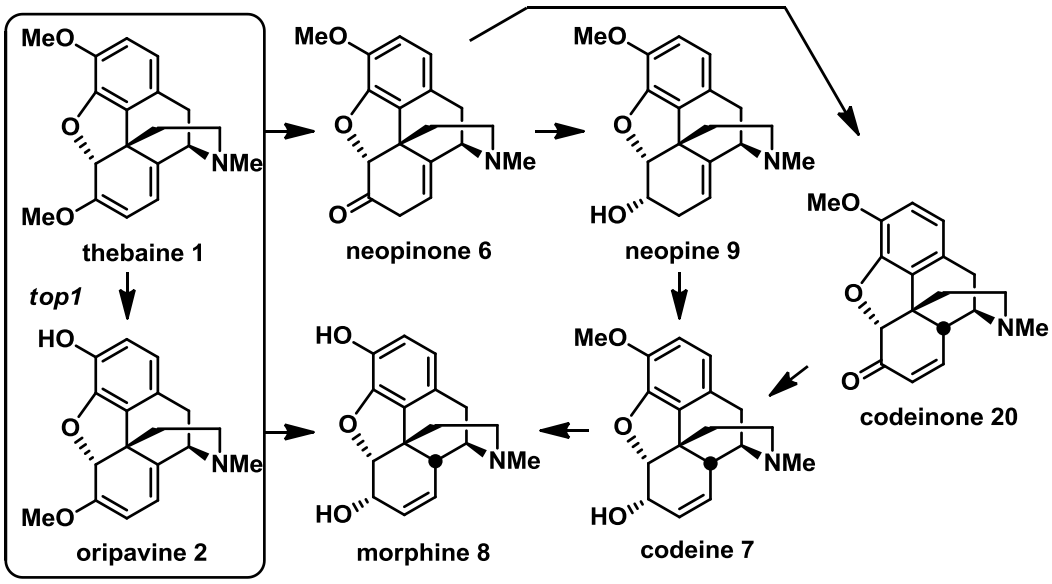
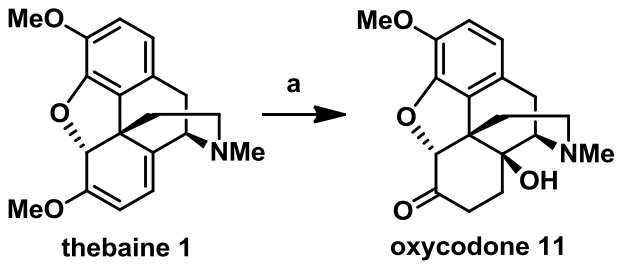



Figure 5. Biosynthetic intermediates *en route* to morphine.

The *Top1* strain was engineered by way of chemical mutagenesis of the opium poppy plant and selected over several generations. The accumulation of thebaine and oripavine, instead of codeine and morphine is very useful since thebaine and oripavine have no appreciable psychoactive profiles, yet serve as indispensable starting materials in the production of any semisynthetics[6,9,10] other than heroin, Figure 5.

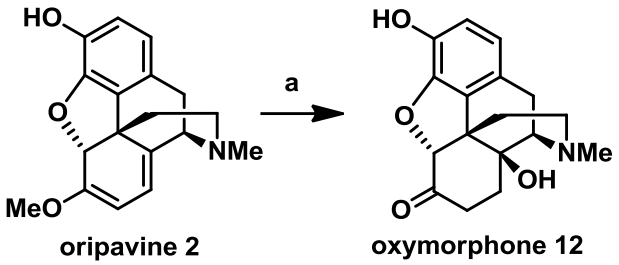
### 2.1.1 Thebaine and oripavine as precursors for semisynthesis

The inherent reactivity of the dienol ether moiety in **1** and **2** is utilized in the production of semisynthetic opiate-derived therapeutic agents. Oxidation or Diels-Alder chemistry is easily performed on the C ring of the thebaine/oripavine system. Such products may thus be carried onward toward oxymorphone, naloxone, buprenorphine, etc.[4,6]




Scheme 1. Conversion of thebaine to oxycodone.
a) (i) AcOH, 30% $H_2O_2$(aq), rt. (ii) Pd/C, $H_2$ (45 psi), rt, 95% yield (two steps).

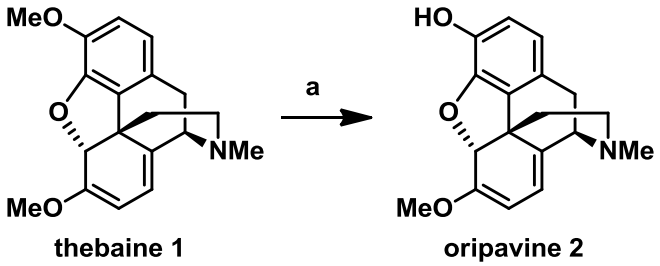
The C-6-ketone and 14-hydroxyl functional groups that appear in such materials as oxycodone are prepared by means of well-documented and predictable chemistry, Scheme 1.[10,11]




Scheme 2. Conversion of oripavine to oxymorphone.
a) (i) AcOOH, AcOH, $H_2O$, rt. (ii) Pd/C, $H_2$ (60 psi), 90 °C, 95% yield (2 steps).

However, the demethylation of the 3-*O*- and 17-*N*-positions are not simple operationally, and especially not if preservation of the dienol ether moiety in the C ring is intended.

The only single step procedure yet disclosed to produce oripavine from thebaine was accomplished using L-selectride in THF at reflux, Scheme 3.[12]




Scheme 3. Direct conversion of thebaine to oripavine.
a) excess L-selectride, THF, reflux, two weeks, 35% yield.

Unfortunately, the high price of L-selectride, the exceedingly long reaction time, and the poor yield[13] have demanded the search for an alternative. To aggravate

the issue, remaining chemical systems to achieve cleavage of an aryl methyl ether rely on strongly acidic (Lewis and/or Brønsted) or basic conditions at very high temperatures.[14] The primary reason for avoidance of acidic demethylation of thebaine lies in the prevention of hydrolysis of the vinyl ether to codeinone **20**, or more severe rearrangements, such as the apomorphine rearrangement, Path A, Figure 6.[15]

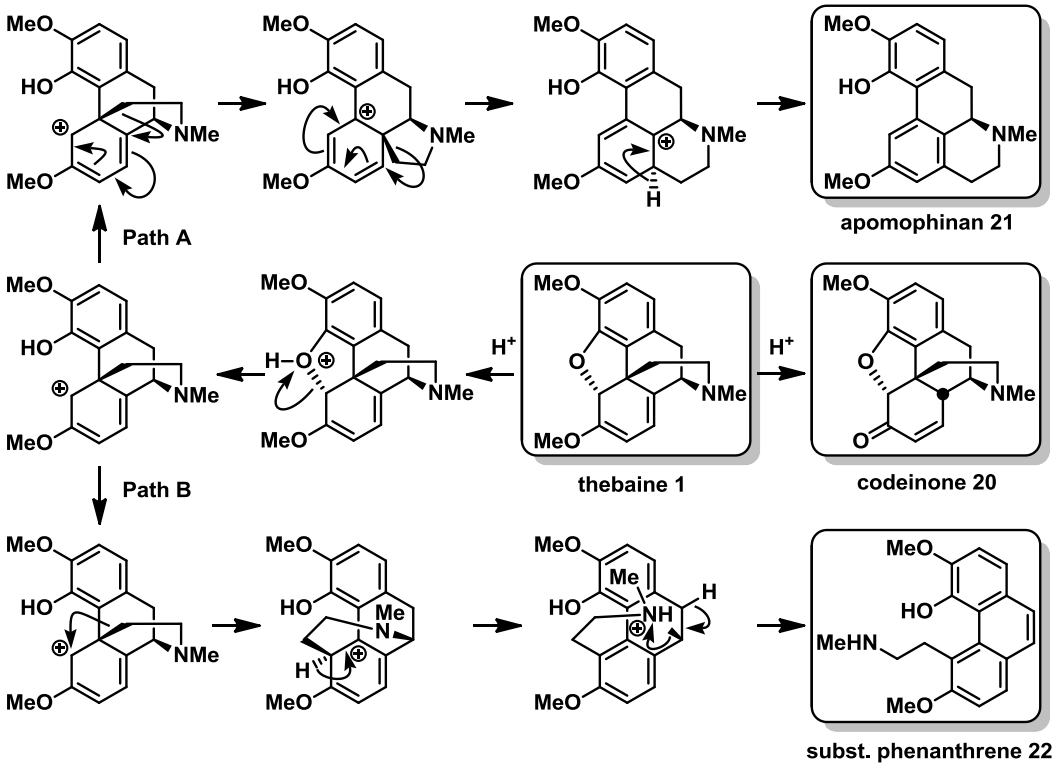
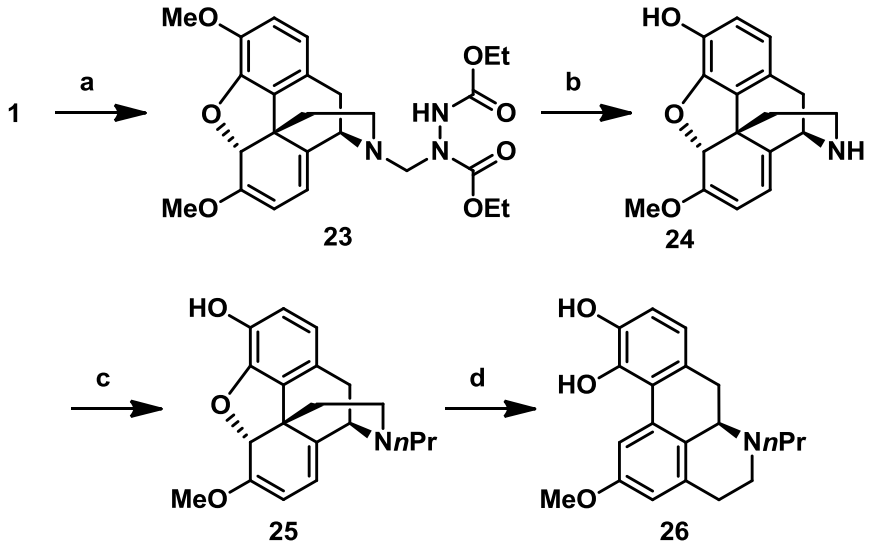



Figure 6. Acid-catalyzed rearrangements of thebaine/oripavine.

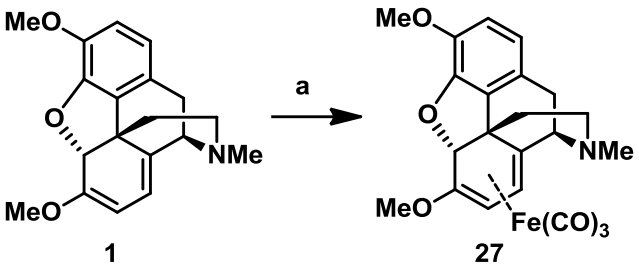
Protonation of the E ring's ether linkage leads to an unraveling of the C and D rings by alkyl migration and eventual aromatization to either an apomorphine **21** or phenanthrene **22** scaffold. Interestingly, the application of the apomorphine rearrangement has found use in the preparation of dopaminergic drug, **26**, development, Scheme 4. First, azodicarboxylate oxidation to **23** and subsequent 3-O-demethylation according to Rice's protocol provided **24**, the "holy grail" of morphinan synthetic intermediates, oripavidine (nororipavine).[16]




Scheme 4. Synthesis of oripavidine and apomorphine analogue.
a) DEAD, PhMe, reflux, 67%; b) excess L-selectride, THF, reflux, 64%; c) *n*PrOH, $NaHCO_3$, $[Cp^*IrCl_2]_2$, µW, 140 °C, 70%; d) $MeSO_3H$, 95 °C, 79%.

In order to prevent acid-promoted rearrangements of the C ring, two schemes were seen as reasonable precedents for implementing reasonable protecting strategies (depending on selective and reversible reactivity). Based on

Birch's work, thebaine's C ring may be complexed as an iron tricarbonyl, Scheme 5,[17] which imparts a reactivity profile similar to an aromatic and/or an aliphatic system.

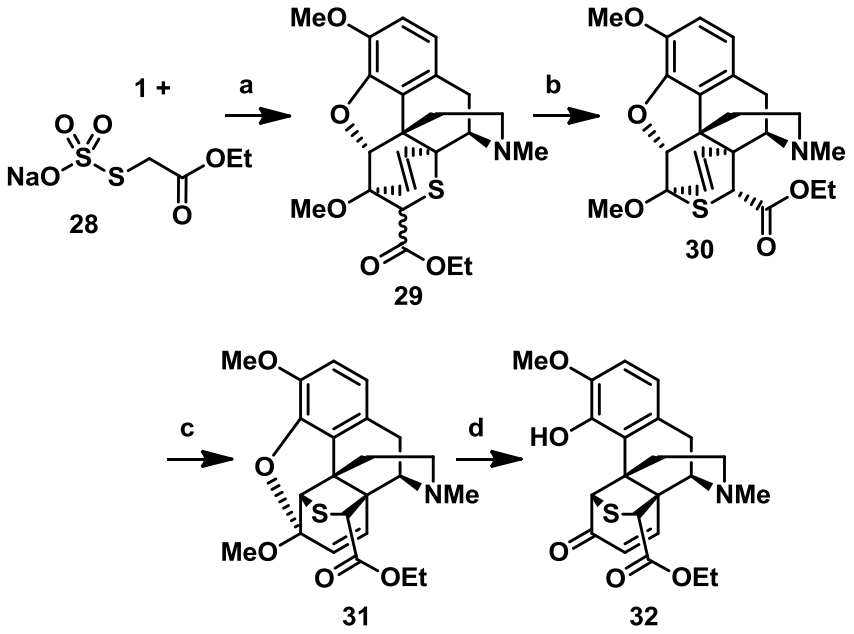



1 27

Scheme 5. Dienol ether protection with iron carbonyl.
a) $Fe_3(CO)_{12}$, $C_6H_6$, reflux; *or* $Fe(CO)_5$, $C_6H_6$,UV light.

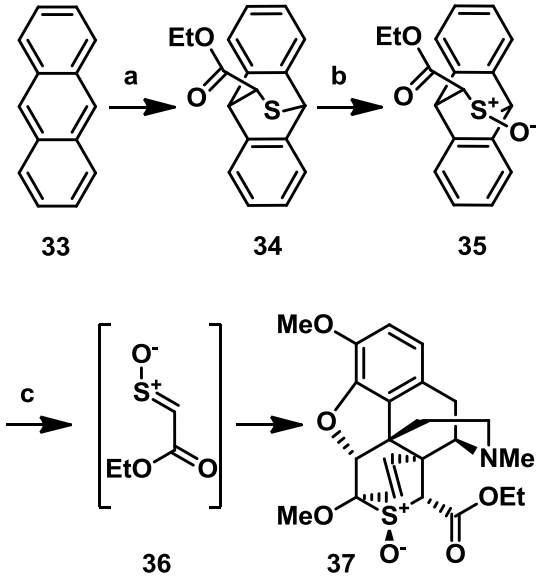
The iron carbonyl complex may be removed under mild oxidative conditions to regenerate the dienol ether in the C ring.

Kirby and coworkers explored the use of thioaldehydes with several dienes,[18] but prominently, thebaine presented an interesting case, in which intermediates rearranged upon prolonged heating, Scheme 6.[19] The enrichment of the thermodynamic product **30** from the initial scalemic product **29** signified a reversibility of the




Scheme 6. Thioaldehyde-Diels-Alder to thebaine and rearrangements thereof.
a) $NEt_3$, $CaCl_2 \cdot 2H_2O$, [EtOH/$C_6H_6$ (1:1)], rt; b) PhMe, reflux, 8 h; c) PhMe, reflux, 160 h; d) conc. HCl, reflux.

hetero-Diels-Alder cycloaddition, whereby the thioaldehyde may be trapped under certain conditions, Scheme 6. Kirby's group further explored exchange of thioaldehydes from the anthracene-adduct **34** and found that heating the sulfoxide **35** led to the transient sulfine (thioaldehyde *S*-oxide) intermediate **36**, which cyclized diastereoselectively with thebaine to provide the chiral sulfoxide **37**.[20]




Scheme 7. Sulfine cycloaddition to thebaine.
a) **28**, $NEt_3$, $CaCl_2 \cdot 2H_2O$, [EtOH/$C_6H_6$ (1:1)], rt; b) *m*CPBA, $CH_2Cl_2$, rt; c) thebaine, $C_6H_6$, 80 °C.

The existing literature on reversible cyclohexadiene transformations provided valuable insight that would be applied to the 3-O-demethylation of thebaine in order to prepare oripavine *vide infra*, as described in the Discussion Section of this thesis.

2.2 The use of *ipso*-diol derived from benzoic acid in organic synthesis

As new reaction development slows and complex natural products discovery continues, innovative alternative chemical processes have emerged. The use of biochemical metabolites in synthesis has been gaining traction of the past couple of decades. Some microorganisms have evolved to metabolized aromatic compounds in their environment. Mutant strains of bacteria have been engineered to accumulate diene-diol chemical entities. *Ralstronia eutrophus* B9 is such a mutant in which (dihydroxybenzoate) DHB dehydrogenase is no longer expressed, Figure 7.[21,22] Isolation of this chiron **4**, is an excellent starting point for synthesis of more complex molecules.[23]

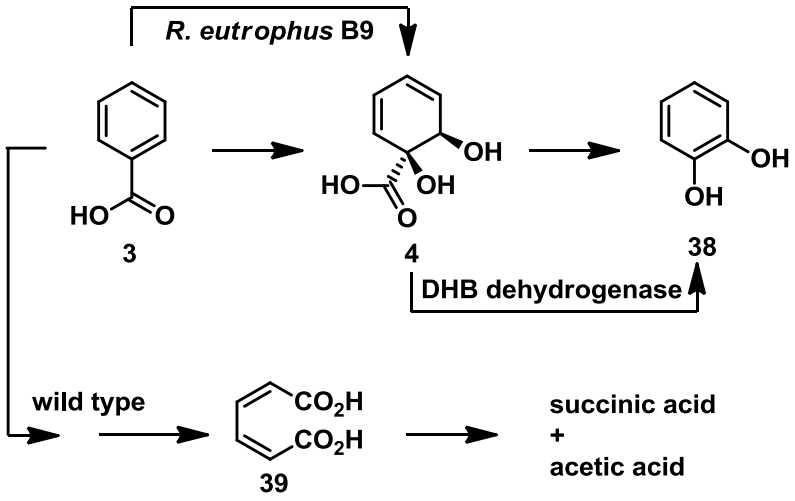
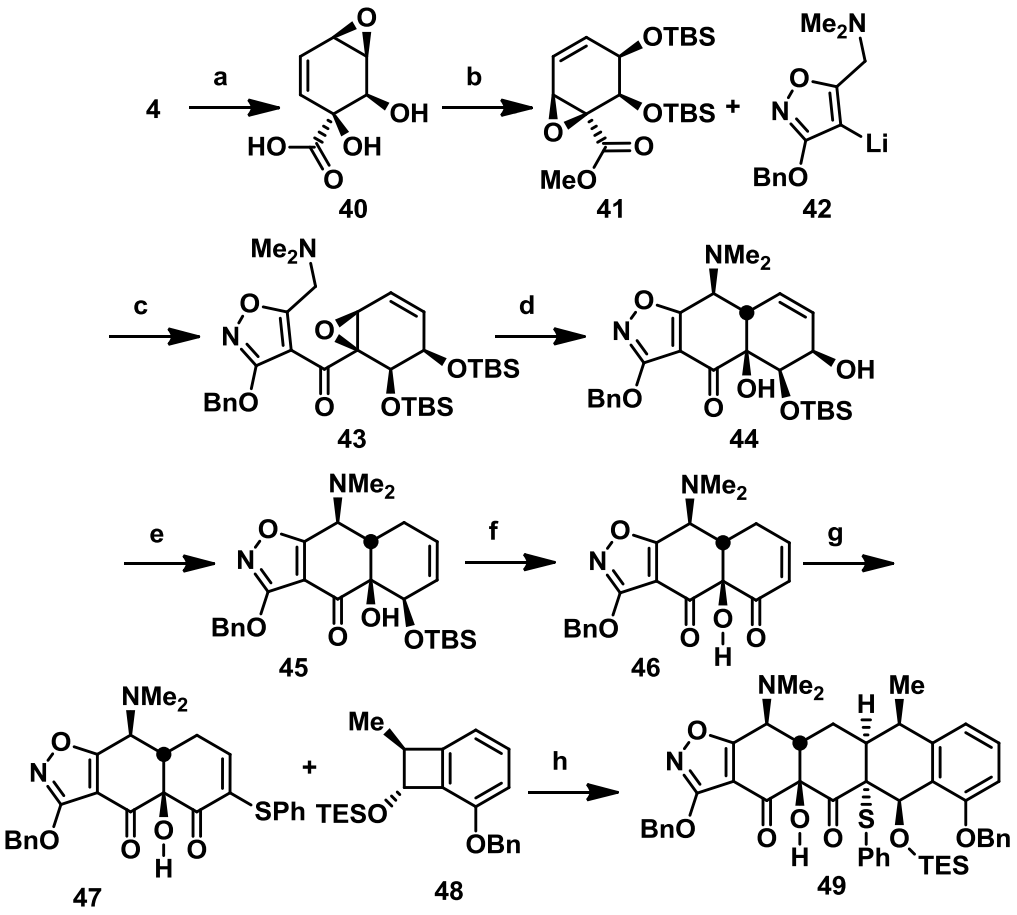



Figure 7. Microbial pathway for benzoic acid degradation.

Though the metabolite was characterized over 40 years ago, it has not been utilized in total synthesis campaigns until the past 10 years.[24]

### 2.2.1 Enantioselective natural product syntheses from benzoic acid

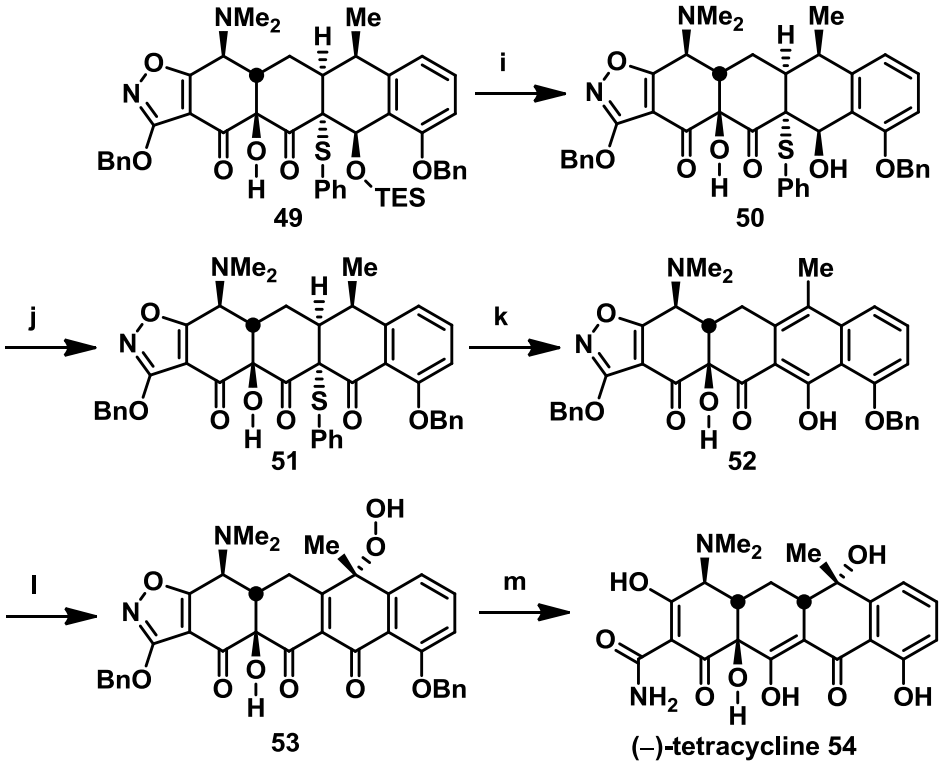
The first and most complex incorporation of the unique *ipso*-diol **4** into a synthetic sequence was accomplished by Myers and co-workers in their total synthesis of (–)-tetracycline, Schemes 8 and 9,[25,26] and analogs thereof. First, hydrogen-bonding-directed epoxidation furnished **40**, followed by carboxylate protection as the methyl ester, and TBS protection interrupted by a Payne rearrangement leading to the chiral electrophile **41**. Addition of the lithiated isoxazole **42** to the methyl ester **41** provided the ketone **43**. An unusual Sommelet-Hauser rearrangement of **43** closed the A ring to supply **44** with correct stereochemistry. Reductive transposition, followed by deprotection of **45** and subsequent oxidation provided enone **46**. Activation with pyridinium tribromide and displacement with thiophenol provided the activated cycloaddition partner **47**, Scheme 8. The mercapto enone and benzocyclobutane **48** were heated together without solvent to form the linear tetracyclic core **49**, Scheme 9.




Scheme 8. Total synthesis of tetracycline from benzoic acid diol. Part 1. a) *m*CPBA, EtOAc, 83%; b) (i) $TMSCHN_2$, $Et_2O$; (ii) TBSOTf, $NEt_3$, 70% (2 steps); c) THF, –78 °C; d) (i) LiOTf, PhMe, 60 °C; (ii) TFA, $CH_2Cl_2$, 62% (2 steps); e) NBSH, DEAD, $PPh_3$, PhMe, 74%; f) (i) HCl, MeOH; IBX, DMSO, 66% (2 steps); g) (i) $HPyr{\cdot}Br_3$, $CH_2Cl_2$; (ii) PhSH, DBU, DMF, 66% (2 steps); h) neat, 85 °C.

The silyl-protected alcohol **49** was unmasked and then oxidized to yield the diketone, whose sulfide was oxidized with a peroxyacid and released upon heating. On exposure to air, napthol **52** was spontaneously oxidized to the

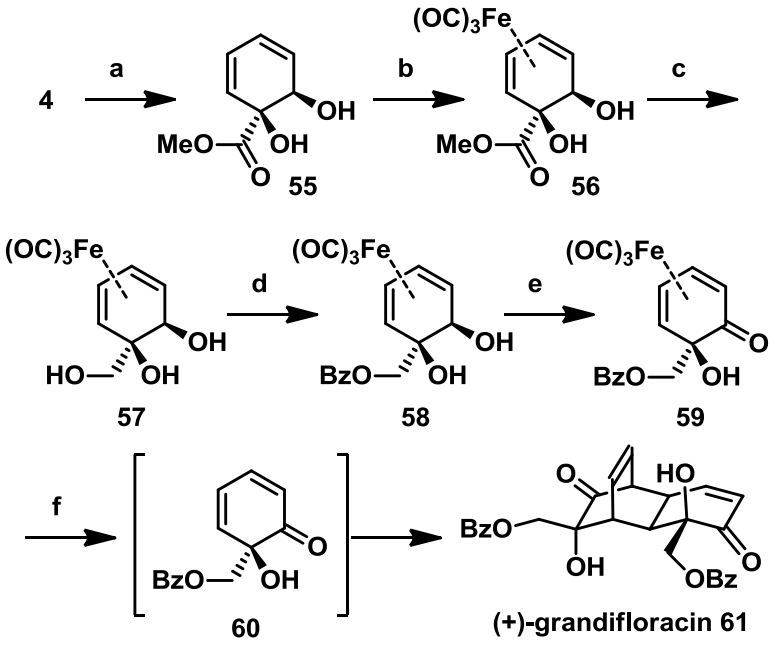
hydroperoxide derivative **53**, which was then immediately reduced under hydrogen atmosphere to yield tetracycline **54**, identical in properties to natural tetracycline.




Scheme 9. Total synthesis of tetracycline from benzoic acid diol. Part 2. i) $NEt_3 \cdot 3HF$, THF, 23 °C, 76%; j) IBX, DMSO, 35 °C, 77%; k) TFA, *m*CPBA, $CH_2Cl_2$, –78 °C to 35 °C; l) $O_2$, spontaneous; m) Pd/C, $H_2$, dioxane, 42% from **51** (sulfide-diketone).

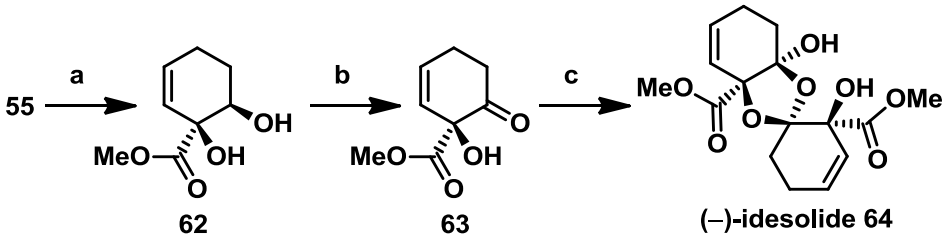
In 2011, Lewis and coworkers[27,28] showed that the cyclohexadiene moiety in **55** could be retained through a series of reductions and oxidations. The dienone, **59**, which upon oxidative cleavage of the iron tricarbonyl led to **60**, and its

spontaneous dimerization to provide the final product **61**, whose attainment served to establish the absolute stereochemistry of the natural product, (–)-grandifloracin.




Scheme 10. Total synthesis of *ent*-grandifloracin.
a) $TMSCHN_2$, MeOH, PhH, 90%; b) $Fe_2(CO)_9$, THF, 77%; c) DIBAL, THF, $CH_2Cl_2$, –78 °C to 20 °C; d) BzCl, collidine, THF, 57% (two steps); e) $MnO_2$, 4Å MS, $CH_2Cl_2$, 78%; f) CAN, acetone, 0 °C, 34%.

Through a similar pattern recognition of dimerization, the unsaturated ketol **63** was prepared by the Hudlicky group[29] through hydrogenation and subsequent oxidation. When exposed to base, ketol 63 furnished stereoselectively the spiroketal dimer, namely idesolide **64**.




Scheme 11. Total synthesis of idesolide.
a) PAD, AcOH, MeOH, 0 °C, 40%; b) IBX, DMSO, 59%; c) $NaHCO_3$, $CHCl_3$, 43%.

This chemoenzymatic approach represents the best synthesis so far of idesolide,[29] which possesses many interesting biological activities.[30,31]

In addition to the above total syntheses, below are some other novel molecules that were prepared from the *ipso*-diol **4**.[32,33] The polyhydroxylated pyrrolidine **65** was prepared as a new nucleoside fragment as an avenue for antiviral therapy,[32] and the inositol-amino acid **66** was prepared out of interest for the fusion of two distinct biological motifs.[34] The cyclohexenol 67 was prepared by way of an oxygen Diels-Alder.[35] These chemical entities would otherwise be very difficult or impossible if it were not for the chemoenzymatic first step.

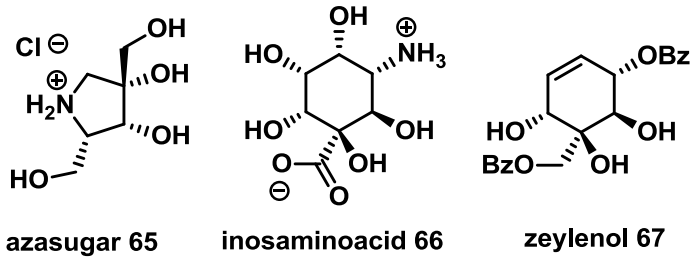



Figure 8. Unusual synthetic products from chemoenzymatic syntheses.

Phenolic glycosides bearing highly oxygenated cyclohexenones have recently been demonstrated to participate in the treatment of malaria, chikungunya, and dengue.[36,37] Even though the compound, xylosmin **5**, has been known for over 20 years,[38] and several recent discoveries of similar compounds **68** and **69** have demonstrated their niche biological potential as therapeutics,[39] no synthesis of the unusual cyclohexenone fragment has yet been reported.

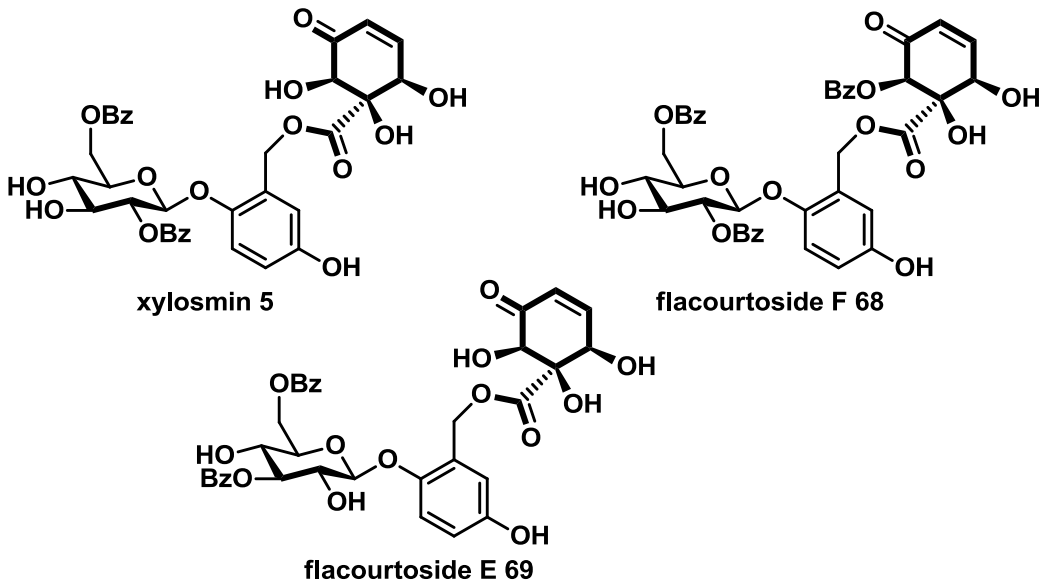



Figure 9. Natural products bearing the highly oxidized cyclohexenone-carboxylate fragment.

The unusually oxygenated cyclohexenone in xylosmin inspired a project to synthesize the fragment, as will be described in the following discussion.

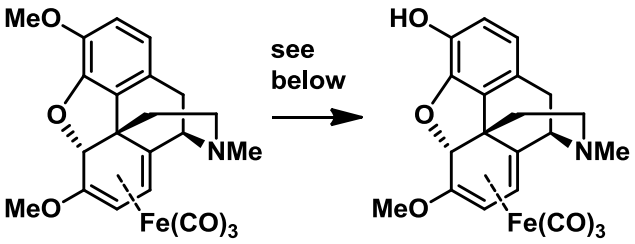
# 3. RESULTS & DISCUSSION

## 3.1 O-Demethylation of thebaine to oripavine

In an effort to generalize the preparation of semisynthetic orvinol-derived pharmaceuticals from the readily available alkaloid thebaine, two strategies of protection, demethylation, and deprotection were used to produce oripavine.

### 3.1.1 C-Ring protection with iron carbonyl

Birch's protocol[17,40] was used to generate thebaine-iron-tricarbonyl complex, isolated in nearly quantitative yield by Dr. Šnajdr. From this point many chemical conditions were applied to unmasking the free phenol of the A ring. To do so, acidic conditions were chosen as basic (nucleophilic) systems[14] were incompatible with the iron tricarbonyl functionality, Table 1.




27 70

| Entry | Conditions | Result |
|---|---|---|
| 1 | $BBr_3$, $CH_2Cl_2$, 0 °C[41,42] | 83% |
| 2 | $BF_3{\cdot}SMe_2$, $CH_2Cl_2$ 0 °C[43] | 83% |
| 3 | $MeSO_3H$, methionine, 50 °C[44] | 67% |
| 4 | 9-I-9-BBN, $CH_2Cl_2$, rt[45] | 70% |

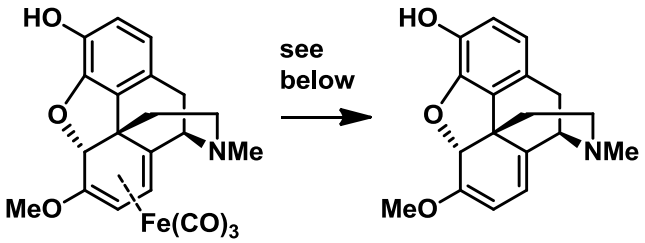
| | | |
|---|---|---|
| 5 | $NbCl_5$, $CH_2Cl_2$, rt[46,47] | decomp. |
| 6 | $NbCl_5$, DCE, reflux[46] | decomp. |
| 7 | HBr (conc.), reflux | no rxn |
| 8 | TMSI, MeCN, reflux[48] | no rxn |
| 9 | TMSCl, NaI, MeCN, reflux[48] | no rxn |
| 10 | $CeCl_3 \cdot 7H_2O$, NaI, MeCN, reflux[49] | no rxn |

Table 1. O-Demethylation Studies of thebaine-iron-carbonyl complex.

Standard aryl methyl ether dealkylation conditions were used at first, i.e. $BBr_3$, with a few more unusual ones, $MeSO_3H$/methionine, or 9-I-9-BBN surfaced as effective. With a few successful chemical conditions established, there had to be addressed the enormous instability of oripavine-iron-carbonyl complex **70**. During many attempts to workup the reaction mixture, complete decomposition would ensue upon reaching pH = 8. Decomposition was characterized by visible turning of the orange solution to a suspension of black ash or rag within seconds of the aqueous phase becoming alkaline. Eventually, with more careful measurements of the volumes and concentrations used, a calculated pH = 7.4 gave optimal product partitioning into the organic phase [$CHCl_3$/*i*PrOH (9:1)] with minimal decomposition of the iron-complexed amino acid morphinan.

Once a viable workup procedure for oripavine iron complex **70** had been developed, many more reaction conditions were tried to decomplex the iron tricarbonyl without oxidation of the phenolic A ring or acidic hydrolysis of the C

ring. This step proved to be most difficult, only a few occasions did recognizable oripavine emerge.




70 2

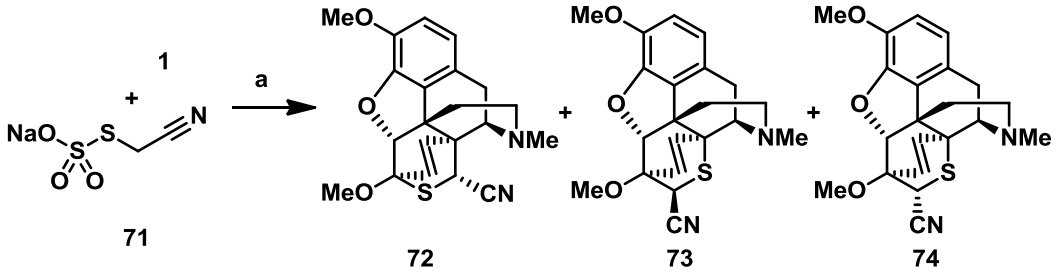
| Entry | Conditions | Result |
|---|---|---|
| 1 | TMANO, MeOH | decomp. |
| 2 | CAN, MeOH[50] | decomp. |
| 3 | $CuCl_2$, EtOH | decomp. |
| 4 | $FeCl_3$, EtOH | decomp. |
| 5 | UV, MeCN[51] | 35% |

Table 2. Iron tricarbonyl decomplexation of oripavine.

Unfortunately, the deprotection step was poor in yield and sensitive to reaction time, challenging the consumption of starting material, yet not leading to decomposition of the newly formed product. Given the rather disappointing results with the decomplexation protocols we turned to Kirby's method of reversible Diels-Alder reaction as means of protection of the diene system in thebaine.

### 3.1.2 C-Ring protection as thiopyran

Thioaldehyde cycloaddition is still a relatively unexplored method for heterocyclic synthesis. The reactive diene of thebaine was reacted with the thioaldehyde derived from **71** leading to the dihydrothiopyran adducts shown in Scheme 12.




Scheme 12. Thebaine to oripavine through a thioformyl protection strategy. a) $NEt_3$, $CaCl_2 \cdot 2H_2O$, [MeOH/$C_6H_6$ (1:1)], **72**:**73**:**74** 1:4.2:3.2, 80%.

The [2.2.2]bicyclic products were separated by column chromatography for individual characterization. The minor compound **72** formed appropriate crystals for X-ray diffraction studies, Figure 10. This regioisomer was never carried to the next sequence of transformational studies.

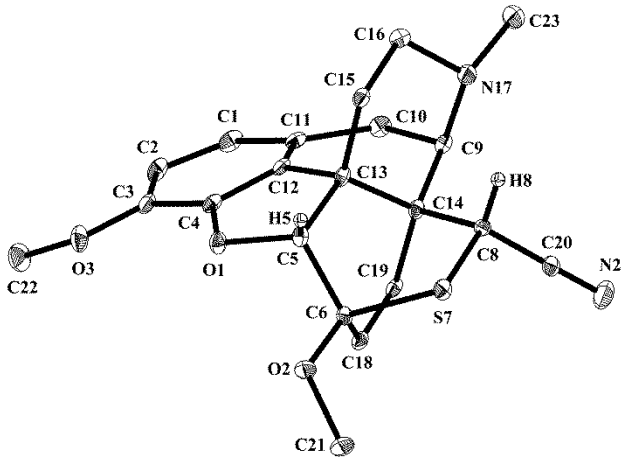
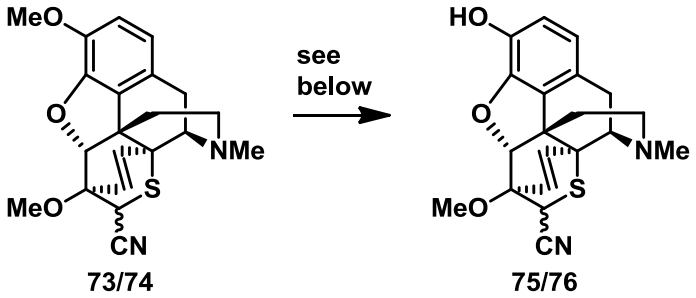



Figure 10. Labeled representation of one of the two crystallographically-independent molecules of **72** in the unit cell.

Each of the two major isolated dihydrothiopyran adducts **73**/**74** (epimeric) were subjected to identical 3-O-demethyation conditions for easy monitoring and characterization of products in the event of success.

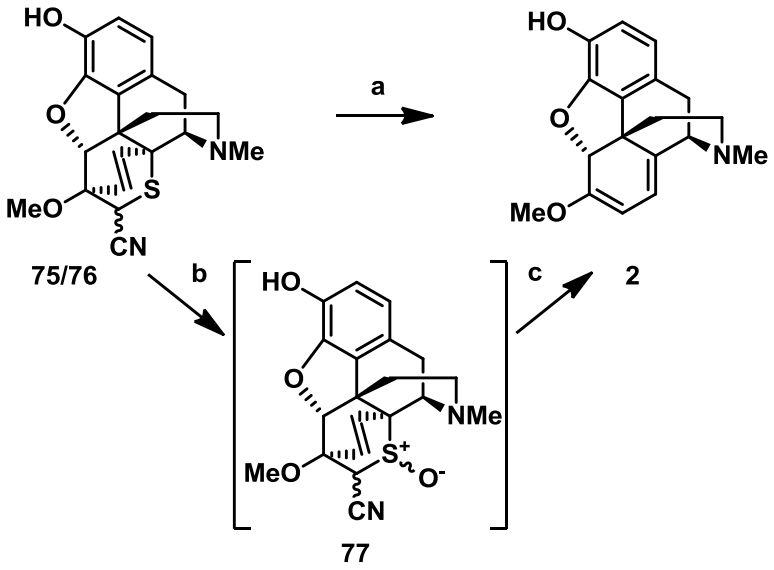



| Entry | Conditions | Result |
|---|---|---|
| 1 | $BBr_3$, $CH_2Cl_2$, 0 °C | 85% |
| 2 | $BF_3{\cdot}SMe_2$, $CH_2Cl_2$ 0 °C | 50% |
| 3 | $MeSO_3H$, methionine, 50 °C | 51% |
| 4 | 9-I-9-BBN, $CH_2Cl_2$, 20 °C | 72% |
| 5 | Dodecanethiol, NaOMe, DMF, reflux | decomp. |

| | | |
|---|---|---|
| 6 | $NbCl_5$, $CH_2Cl_2$, rt | decomp. |
| 7 | $NbCl_5$, DCE, reflux | decomp. |
| 8 | TMSI, MeCN, reflux | no rxn |
| 9 | TMSCl, NaI, MeCN, reflux | no rxn |
| 10 | $CeCl_3 \cdot 7H_2O$, NaI, MeCN, reflux | no rxn |

Table 3. 3-O-Demethylation studies of dihydrothiopyrans.

Once O-demethylation conditions were established, (interestingly, their attainment coincided with the successful deprotection of the iron carbonyl complexe), the final deprotection was accomplished in a relatively easy chemical sequence. The published procedures by Kirby[18–20] indicated the reversibility of the thioaldehyde cycloaddition, which was exploited below, Scheme 13, in two different ways.




Scheme 13. Dihydrothiopyran cycloreversion to produce oripavine. a) 2,3-Dimethylbutadiene (20 eq.), DMSO, 75 °C, sealed tube, 65%; b) *m*CPBA, $CH_2Cl_2$, rt; c) EtOH, reflux, 78% (2 steps).

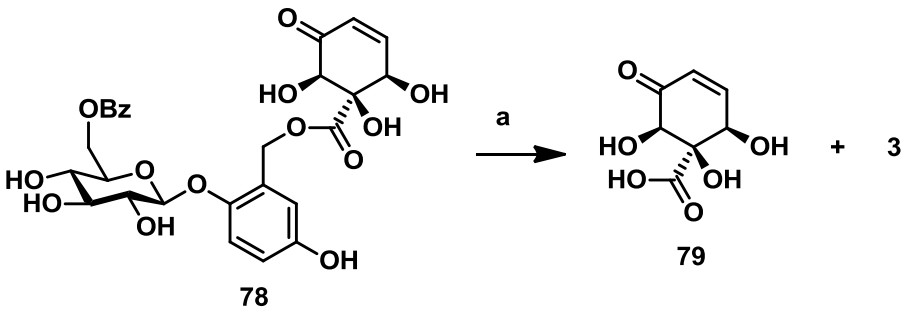
Thermal cycloreversion and competitive capture of the thioaldehyde by a diene was first attempted, though it proved to be not ideal ase the use of an emulsifying solvent and sealed tube conditions complicated handling. The conversion to oripavine was never observed to reach completion. To obviate this problematic equilibrium of competitive Diels-Alder reactions and the possibility of polymerization of the thioaldehyde scavenger, the dihydrothiopyran **75** or **76**, was oxidized to the sulfoxide **77**, which was then heated to extrude a thioaldehyde-*S*-oxide that was easily captured *irreversibly* by the solvent. This condition led to greater yields and simpler product isolation, though they did

require the use of exactly one molar equivalent of *m*CPBA, because of concerns with possible over oxidation at *N*-17.

This newly developed sequence of transformations was again applied to thebaine with the aim of yield optimization. Through three telescoped steps with no isolation isomeric intermediates, oripavine was prepared in an overall yield of 44% from thebaine with one chromatographic purification.[52]

3.2 Chemoenzymatic synthesis of a *flacourtia* aglycone methyl ester

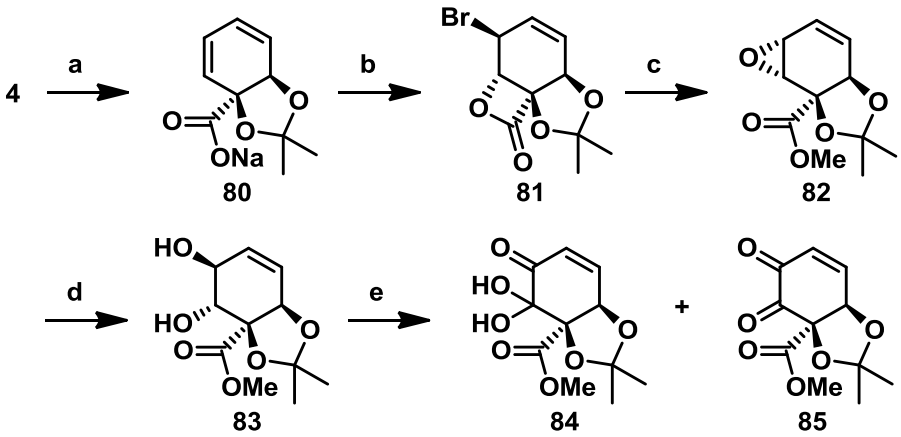
The aglycone was seen though pattern recognition as an entity that could be derived from the chemoenzymatic oxidation of benzoic acid. The aglycone fragment,[36–39] bearing a strange array of oxidation, teetering on the edge of aromatization, had never before been synthesized, so its pursuit as a target seemed worthy.




Scheme 14. Hydrolysis of flacourtoside. a) $Ba(OH)_2 \cdot 8H_2O$, $H_2O$, reflux.[37]

Through a process first described by Myers[53] and Banwell,[54] and further refined by Dr. Adams of the Hudlicky group[55], the β-lactone **81** was reliably prepared, albeit in persistently low yields. From the known vinyl epoxide **82**, a straight forward set of oxidations was seen as a means to arrive at the desired aglycone **79**, Scheme 15. By selective opening of the vinyl epoxide with water at the allylic position (without acetonide or methyl ester loss),[56–59] the allylic alcohol of **83** could then by oxidized using the historically selective $MnO_2$.

3.3 Attempted synthesis of *flacourtia* aglycone **79**.

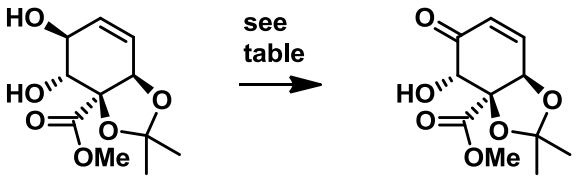



Scheme 15. Attempt one at synthesizing the *flacourtia* fragment. a) TFA, 2,2-DMP, 0 °C, 84%; b) $Br_2$, $NaHCO_3$, $CH_2Cl_2$, $H_2O$, 0 °C, 45%; *or* NBS, $CH_2Cl_2$, PhMe, 20 °C, 85%; c) NaOMe, MeOH, 0 °C, 79%; d) 5% $Bi(OTf)_3$, $H_2O$, MeCN, 20 °C, 72%; e) $MnO_2$, EtOAc, 20 °C, 60%.

The consistent appearance of the over oxidation product **84**/**85** forced the exploration of more exotic and "selective" allylic alcohol oxidation conditions, as shown in Table 4.

DDQ is an effective oxidant of cyclic systems resembling the same allylic 1,2-diol present in **83**. However, while performing the reaction, no progress was seen at room temperature, and so other reagents and conditions were explored. [*A solution for this oxidation was eventually found by simply heating the reaction mixture with DDQ. In hindsight, this may have been the best course of action from the start; suffice it to say that the hunt for these successful conditions took almost two months of effort*]. Venturing onward to riskier oxidations, IBX in DMSO was tried, though these conditions resulted in full decomposition to chromatographically inert material. The propensity of 1,2-diol oxidation by C-C bond cleavage is documented, especially on strained cyclic systems.[60]

The use of catalytic *N*-oxyl radicals as selective oxidizing agents has recently grown in popularity, though when applied to this case, the use of PIFA was presumed to have led to the same oxidative cleavage of **83** as observed by IBX.




**83** **86**

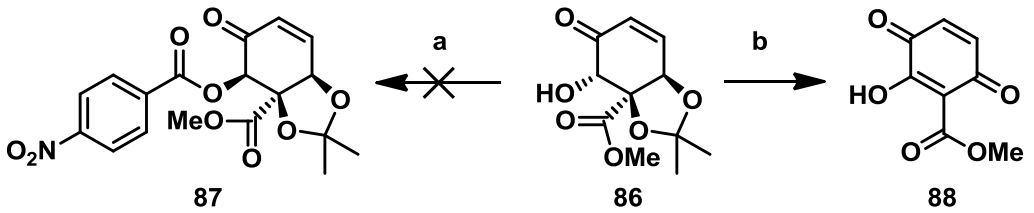
| Entry | Conditions | Result |
|---|---|---|
| 1 | DDQ, EtOAc, rt[61] | no rxn |
| 2 | IBX, DMSO, rt | decomp. |
| 3 | PIFA, $K_2CO_3$, AZADO, MeCN, $CH_2Cl_2$, rt[62] | decomp. |

| | | |
|---|---|---|
| 4 | 4-MeO-$C_6H_4$-$B(OH)_2$, DBI, $H_2O$, 0 °C, (dark)[63] | no rxn |
| 5 | IBX, [bmim]Cl, $H_2O$, rt, 3h[64] | 65% |

Table 4. Selective oxidation of an allylic 1,2-diol.

A recently published procedure reported the use of catalytic *p*-anisole boronic acid and stoichiometric DBI in the dark, appeared- at least on paper-to be promising, though after conducting the reaction twice, no progress was observed. Finally, in a desperate fancy, IBX was revisited, but this time in an ionic liquid, 1-butyl-3-methylimidazolium chloride, [bmim]Cl. With some surprise, the acyloin **86** was isolated as a white solid after careful removal of the ionic liquid.

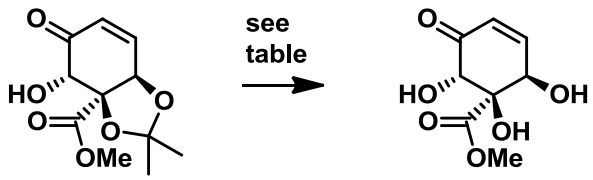
With all atoms in the correct oxidation state, all that remained was the epimerization of the ketol **86** and deprotection. While it was speculated at the beginning that epimerization should ensue spontaneously to the natural diastereomer **79**, no such isomerism was observed. Two different methods were employed to effect this stereochemical inversion, Scheme 16, but none succeeded. Mitsunobu reaction performed by the preformation of the phosphonium imide, cannulation to the ketol **86**, followed by addition of *p*-nitrobenzoic acid was also met with no success.




Scheme 16. Attempted α-Hydroxy-ketone inversion.
a) DEAD, *n*$Bu_3$P, THF, 4-$NO_2$-BzOH, 0 °C to rt; b) TMSCl, $NEt_3$, THF, 0 °C, then DBU.

Another attempt began with silyl ether formation and subsequent enolization with expected equilibration to the natural (more stable) diastereomer; this, however, led to an unforeseen ejection of the tertiary acetonide bond, driven by aromatization. The resulting 2,3,6-trihydroxy methyl benzoate was oxidized by atmospheric oxygen to the *p*-quinone **88**. The mass spectrum of this compound very closely resembled the fragmentation pattern of 2,3,4-trihydroxy methyl benzoate, though $^{13}$C-NMR presented contradictory chemical shift data. The exact identity of this unexpected product remains unconfirmed.

Accepting the lack of success to force the isomerization, we turned to acetonide removal through acidic solvolysis to provide the α,β,γ-trihydroxy cyclohexenone. Unfortunately, such processes only led to decomposition. This transformation, though mundane, was unsuccessful and led only to complete loss of reaction contents, Table 5.




86 89

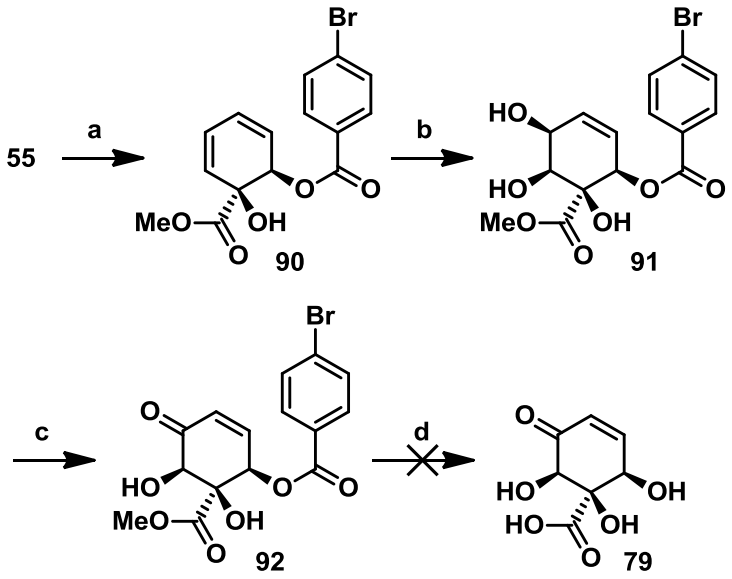
| Entry | Conditions | Result |
|---|---|---|
| 1 | PPTS, $H_2O$, THF | no rxn |
| 2 | $NaHSO_4 \cdot SiO_2$, $CH_2Cl_2$, *i*PrOH | no rxn |
| 3 | $FeCl_3 \cdot SiO_2$, $CHCl_3$ (Kim's Reagent) | no rxn |
| 4 | TFA, $H_2O$, MeCN, 0 °C, 45 min | decomp. |

Table 5. Acetonide removal.

It became quite clear that a better method must be devised to achieve the synthetic goal.

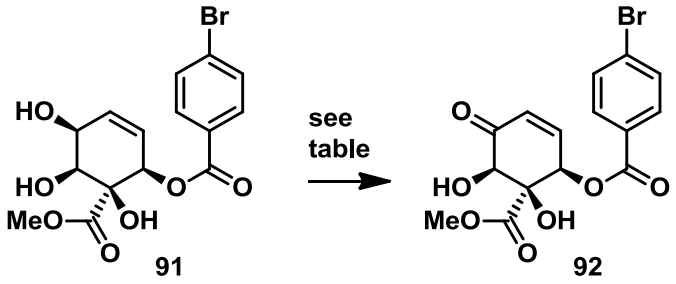
### 3.3.1 Donohoe Dihydroxylation Approach

Reevaluation of the starting material with respect to the target and recent knowledge of a specific methodology empowered a new pathway. Selective protection of the secondary allylic alcohol provided **90**. An H-bond-directed osmium dihydroxylation[65,66] led to triol **91**. The reminiscent allylic alcohol was yet again found to be inexplicably unreactive to oxidizing conditions.




Scheme 17. Attempt two at synthesizing the *flacourtia* fragment.
a) 4-Br-BzCl, TMEDA, $CH_2Cl_2$, –78 °C, 84%; b) $OsO_4$, TMEDA, $CH_2Cl_2$, –78 °C, 93%; c) DDQ, dioxane, 70 °C, 82%; d) LiOH, THF, $H_2O$, decomp.

The previously successful use of IBX in [bmim]Cl led to slow conversions and there was great difficulty in recovering the triol **91** from the ionic liquid reaction medium.




| Entry | Conditions | Result |
|---|---|---|
| 1 | IBX, [bmim]Cl, $H_2O$, rt, 2 days | trace |
| 2 | cat. DDQ, $Mn(OAc)_3 \cdot 2H_2O$, $CH_2Cl_2$, rt, 2 days[67] | trace |

| | | |
|---|---|---|
| 3 | cat. DDQ, $NaNO_2$, $O_2$, AcOH, DMC, rt, 2 days[67] | trace |
| 4 | DDQ, dioxane, 70 °C, 6 days | 80% |

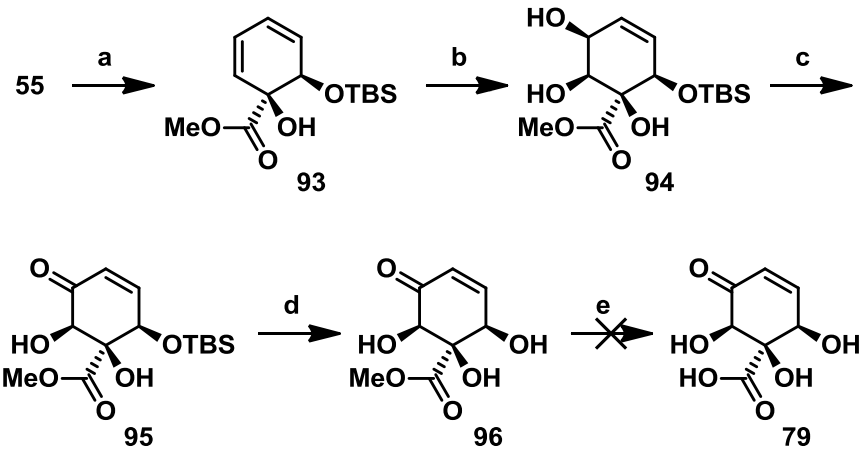
Table 6. Selective allylic oxidation.

Eventually, an effective method for oxidation of allylic alcohols in cyclic systems revealed itself through the use of DDQ. The elevated temperature was necessary to consume starting material in a reasonable amount of time. Later, TLC analysis of saved samples showed that all the oxidation systems previously attempted worked, albeit at very slow rates.

With the ultimate intermediate prepared, the hydrolysis of the halo benzoate and methyl ester was done in sequence to avoid possible decarboxylation. The attempted hydrolysis using LiOH led to *p*-bromobenzoic acid as the only recognizable product. This additional frustration led to the last attempt at the synthesis through the use of a silyl protecting group.

Beginning again with the methyl ester *ipso*-diol **55**, the secondary alcohol was transformed to the silyl ether **93**. Donohoe dihydroxylation led in moderate yield to triol **94**, which was cleanly oxidized to the ketol **95**. Careful cleavage of the silyl ether provided the penultimate material **96**. Saponification with barium hydroxide was executed according to the isolation article.[37] With some suspicion of the procedure's excessive force, compound **96** was dissolved in water and

stirred at room temperature for 2 h. TLC indicated no starting material, yet a yellow baseline spot upon $KMnO_4$ staining.




Scheme 18. Final attempt at the *flacourtia* fragment.
a) TBSCl, imidazole, $CH_2Cl_2$, DMF, rt; b) $OsO_4$, TMEDA, $CH_2Cl_2$, –78 °C; c) DDQ, dioxane, 85 °C; d) AcOH, TBAF, MeOH, 25 °C; e) $Ba(OH)_2 \cdot 8H_2O$, $H_2O$, 100 °C.

These synthetic sequences illustrate the importance of general methodological knowledge and the proper selection of protecting groups as these are needed.

## 4. CONCLUSION & FUTURE WORK

Organic synthesis continues to be a science learnt through empiricism, and rarely proceeds as idealistically predicted. Thebaine was transformed into oripavine through the use of iron(0) complexation or thioaldehyde cycloaddition as a means of cyclohexadienyl-ether protection. While not grabbing the attention of industrial innovators in semisynthetic opiate production, this work contributes to the niche of morphinans and diene protection strategies. Future work in this area includes the *N*-demethylation of thebaine and/or oripavine without the use of cyanogen bromide or chloroformates, as the product, oripavidine (nororipavine) constitutes the progenitor of all morphinan scaffolds of highest therapeutic value.

The *ipso* diol continues to show utility as a valuable chiron for the enantioselective synthesis of complex natural products. The diene-diol was used as a starting material to synthesize the strangely oxidized cyclohexenone aglycone belonging to the phenolglycosidic flacourtoside series. Initial use of the known vinyl epoxide led to a dead end and the approach was reevaluated to have the correct stereochemistry delivered through a Donohoe dihydroxylation. After experimentation with protection strategies and highly selective oxidizing reagents, strong bases and strong acids were more than capable of spurring substrate aromatization or

decomposition. The future is open to new targets derived from the unique *ipso* diol, as organic chemistry becomes ever more selective and clever. Academic organic synthesis strives, and continues to stand for the purpose of furthering the knowledge of carbon-based molecular transformations for the ultimate goal of harnessing Nature's living architecture for the good of humankind.

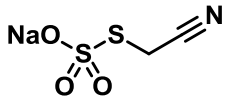
# 5. EXPERIMENTAL

## 5.1 General Experimental Details

All non-aqueous reactions were conducted in an argon atmosphere using standard Schlenk techniques for the exclusion of moisture and air. All solvents were distilled unless otherwise noted. Analytical thin layer chromatography was performed on EMD Silica Gel 60 Å 250 µm plates with F-254 indicator. Column chromatography was performed using Silicycle SiliaFlash P60 (230-400 mesh). Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. Optical rotations were measured on a Mandel Rudolph Research Analytical Automatic Polarimeter at 589 nm with a cell length of 50 mm. IR spectra were obtained on a Bruker ATR FT-IR Spectrometer. $^{1}H$ and $^{13}C$ spectra were recorded on a 300 MHz, 400 MHz, and 600 MHz Bruker spectrometer. All chemical shifts are referenced to TMS or residual non-deuterated solvent. Data for proton spectra are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m)], coupling constants [Hz], integration). Carbon spectra were recorded with proton decoupling and the chemical shifts are reported in ppm (C) relative to TMS. Mass spectra and high resolution mass spectra were performed by the analytical division at Brock University. Combustion analyses were performed by Atlantic Microlabs, Atlanta, GA, USA.

5.2 Detailed Experimental Procedures

**Sodium *S*-(cyanomethyl) sulfothioate, *Bunte salt* (71)**.

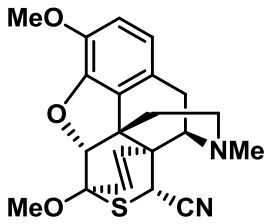


Prepared according to a published protocol.[19] A mixture of $Na_2S_2O_3 \cdot 5H_2O$ (9.97 g, 63 mmol), chloroacetonitrile (5 g, 66 mmol), in [$H_2O$/EtOH (1:1)] (40 mL) was heated at 80 °C for 1 h, then left at room temperature for 18 h. The mixture was cooled to 0 °C and then filtered, and rinsed with EtOH. The product was recrystallized from hot EtOH and dried under reduced pressure to yield (7.06 g, 64%). mp 90-92 °C (EtOH); IR (neat) *v* 3623, 3448, 2966, 2260, 1637, 1209, 1034 $cm^{-1}$.

**Thioaldehyde adduct isomers**, **72**, **73**, and **74**.

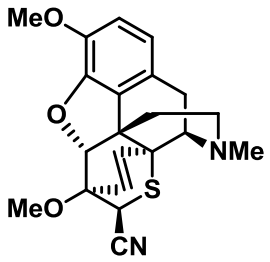
Thebaine (930 mg, 3 mmol), $CaCl_2 \cdot 2H_2O$ (620 mg, 4.2 mmol), and **71** (735 mg, 4.2 mmol) were dispersed in $C_6H_6$ (7 mL) and MeOH (7 mL) and stirred vigorously (large stir bar is necessary). Triethylamine (420 mg, 4.2 mmol) was added drop-wise. After stirring at room temperature for 8 h, the reaction mixture was diluted with EtOAc (20 mL), and then centrifuged for 20 min at 7000 rpm. The supernatant was concentrated under reduced pressure and the crude residue was purified by column chromatography [hexane/EtOAc (2:1)]. Each isomer was crystallized from MeOH, total yield (910 mg, 80%).

**(–)-(4*R*,4a*S*,7*R*,7a*R*,12b*R*,15*R*)-7,9-Dimethoxy-3-methyl-1,2,3,4,7,7a-hexahydro-7,4a-(epithiomethano)-4,12-methanobenzofuro[3,2-e]isoquinoline-15-carbonitrile (72)**.



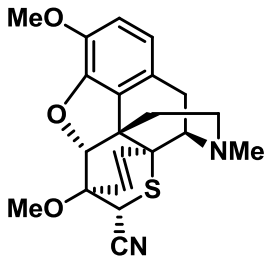

(110 mg, 12%); $R_f$ = 0.73 [hexane/EtOAc (1:1)]; mp 184-185 °C (MeOH); $[\alpha]_D^{20}$ = –319.1° (*c* = 1.0, $CHCl_3$); IR (neat) *v* 2915, 2841, 2797, 2232, 1442, 1050, 869, 817, 795, 592 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 6.66 (d, *J* = 8.2 Hz, 1H), 6.59 (d, *J* = 8.2 Hz, 1H), 6.39 (dd, *J* = 9.1, 1.3 Hz, 1H), 5.66 (d, *J* = 9.1 Hz, 1H), 5.38 (s, 1H), 4.92 (s, 1H), 3.80 (s, 3H), 3.62 (s, 3H), 3.54 (d, *J* = 6.6 Hz, 1H), 3.31 (d, *J* = 18.6 Hz, 1H), 2.55 (dd, *J* = 18.6, 6.6 Hz, 2H), 2.46-2.38 (m, 4H), 2.01-1.93 (m, 1H), 1.90 (dd, *J* = 13.6, 2.9 Hz, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 146.8, 142.2, 133.2, 131.5, 130.9, 126.9, 119.6, 119.1, 113.7, 92.3, 89.9, 59.1, 56.4, 53.9, 47.6, 45.0, 43.5, 36.1, 33.8, 22.8; MS (EI+, *m/z* (rel.%)) 382 (93), 311 (50), 325 (23), 296 (25), 267 (22), 255 (35), 230 (55), 58 (100); Anal. Calcd. for $C_{21}H_{22}N_2O_3S$: 382.14, found 382.13. CCDC #988979.

**(–)-(4*R*,4a*S*,7*S*,7a*R*,12b*S*,14*S*)-7,9-Dimethoxy-3-methyl-1,2,3,4,7,7a-hexahydro-4a,7-(epithiomethano)-4,12-methanobenzofuro[3,2-e]isoquinoline-14-carbonitrile (73).**




(450 mg, 50%); $R_f$ = 0.58 [hexane/EtOAc (1:1)]; mp 145-150 °C; $[\alpha]_D^{20}$ = –218.2° (*c* = 1.0, $CHCl_3$); IR (neat) *v* 2935, 2836, 2792, 2234, 1499, 1279, 1107, 1021, 906, 793 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 6.65 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 5.91 (q, *J* = 9.1 Hz, 2H), 5.00 (s, 1H), 3.83 (s, 3H), 3.77 (s, 1H), 3.67 (s, 3H), 3.39 (d, *J* = 6.6 Hz, 1H), 3.27 (dd, *J* = 18.3, 10.6 Hz, 1H), 2.93 (td, *J* = 12.7, 5.5 Hz, 1H), 2.68 (dd, *J* = 12.2, 5.3 Hz, 1H), 2.53-2.44 (m, 2H), 2.40 (s, 3H), 1.89 (dd, *J* = 13.1, 2.5 Hz, 1H) the proton NMR contains an impurity, likely compound **72**; $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 147.0, 142.5, 138.0, 133.2, 126.6, 124.6, 119.9, 117.4, 114.6, 91.4, 79.9, 60.0, 56.9, 53.9, 52.9, 50.5, 45.8, 43.4, 35.2, 32.7, 23.2; MS (EI+, *m/z* (rel.%)): 382 (7), 311 (95), 297 (50), 255 (22); HRMS (ESI) Anal. Calcd. for $C_{21}H_{22}N_2O_3S$: 382.1351, found 382.1351.

**(+)-(4*R*,4a*S*,7*S*,7a*R*,12b*S*,14*R*)-7,9-Dimethoxy-3-methyl-1,2,3,4,7,7a-hexahydro-4a,7-(epithiomethano)-4,12-methanobenzofuro[3,2-e]isoquinoline-14-carbonitrile (74).**




(350 mg, 38%): $R_f$ = 0.50 [hexane/EtOAc (1:1)]; mp 164-165 °C; $[\alpha]_D^{20}$ = +5.9° (*c* = 1.0, $CHCl_3$); IR (neat) *v* 2948, 2802, 2235, 1500, 1284, 1108, 1019, 894, 760 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 6.66 (d, *J* = 8.2 Hz, 1H), 6.58 (d, *J* = 8.2 Hz, 1H), 6.00 (d, *J* = 8.8 Hz, 1H), 5.95 (d, *J* = 9.0 Hz, 1H), 4.52 (s, 1H), 4.08 (s, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.47 (d, *J* = 6.5 Hz, 1H), 3.26 (d, *J* = 18.5 Hz, 1H), 2.71 (td, *J* = 12.6, 5.5 Hz, 1H), 2.61 (dd, *J* = 12.2, 5.3 Hz, 1H), 2.54 (dd, *J* = 18.5, 6.6 Hz, 1H), 2.47-2.40 (m, 1H), 2.39 (s, 3H), 1.81 (dd, *J* = 12.8, 2.7 Hz, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 146.5, 142.5, 136.4, 133.1, 126.4, 126.4, 120.2, 117.8, 114.1, 90.8, 80.2, 77.3, 77.0, 76.8, 60.1, 56.6, 53.1, 52.5, 50.7, 45.6, 43.3, 35.7, 32.9, 23.2; MS (EI+, *m/z* (rel.%)): 382 (7), 311 (95), 296 (50), 255 (22); HRMS (ESI) Anal. Calcd. for $C_{21}H_{22}N_2O_3S$; 382.1351, found 382.1455.

**O-Demethylated Thioaldehyde adduct isomers 73** and **74**

Method **A**: To a solution of **73** and/or **74** (200 mg, 0.52 mmol) in $CH_2Cl_2$ (10 mL) was slowly added $BBr_3$ (0.780 g, 3.12 mmol) at 0 °C. Reaction was stirred for 20 min at 0 °C and then removed from the ice bath and stirred for another 15 min. The reaction mixture was poured into ice water (20 mL) and acidity was slowly adjusted to pH = 8 with 15% aqueous NaOH. Mixture was extracted with $CH_2Cl_2$ (3 x 10 mL). Combined organic phases were concentrated under reduced pressure and purified by column chromatography [hexane/EtOAC (1:1)] yielding **75** and/or **76** (162 mg, 85%).

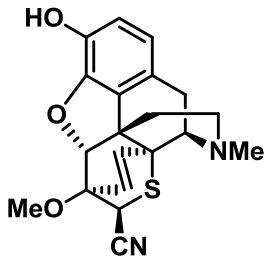
Method **B**: To a solution of **73** (150 mg, 0.4 mmol) in dry $CH_2Cl_2$ (15 mL) was slowly added $BF_3{\cdot}SMe_2$ complex (0.25 mL, 2.36 mmol) at 0 °C. Reaction was stirred for 4 h at 0 °C and then 2 h at room temperature. The reaction was then decanted into ice-water (20 mL) and the acidity was slowly adjusted to pH = 8 with 15% aqueous NaOH. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 10 mL). The organic layers were combined and then washed with brine and dried over $Na_2SO_4$, concentrated under reduced pressure, then purified by column chromatography [hexane/EtOAc 1:1)] to yield **75** (74 mg, 50%).

Method **C**: To a solution of **73** (170 mg, 0.395 mmol) in dry $MeSO_3H$ (1.15 mL, 11.8 mmol) was slowly added *rac*-methionine (90 mg, 0.594 mmol). The orange solution was then heated to 50 °C and left to stir for 8 h. The reaction was

monitored by HPLC. The reaction was then decanted into ice water (20 mL) and the acidity was slowly adjusted to pH = 8 with 15% aqueous NaOH solution. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 10 mL). The organic layers were combined and then washed with brine and dried over $Na_2SO_4$, concentrated under reduced pressure and the product purified by column chromatography [hexane/EtOAc (1:1)] to yield **75** (73 mg, 51%).

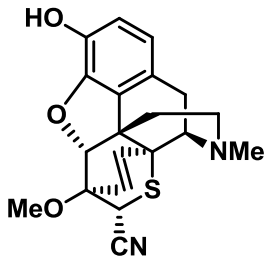
Method **D**: To a solution of **73** and/or **74** (110 mg, 0.287 mmol) in dry $CH_2Cl_2$ (5 mL) was slowly added 9-I-9-BBN (0.86 mL, 1M in hexanes) at room temperature. After 4 h, the reaction mixture was decanted into ice-water (20 mL) and the acidity was slowly adjusted to pH = 8 with 15% aqueous NaOH. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 10 mL). The organic layers were combined and then washed with brine and dried over $Na_2SO_4$, concentrated under reduced pressure, then purified by column chromatography [hexane/EtOAc (1:1)] to yield **75** and/or **76** (80 mg, 72%).

**(–)-(4*R*,4a*S*,7*S*,7a*R*,12b*S*,14*S*)-9-Hydroxy-7-methoxy-3-methyl-1,2,3,4,7,7a-hexahydro-4a,7-(epithiomethano)-4,12-methanobenzofuro[3,2-e]isoquinoline-14-carbonitrile (75)**.



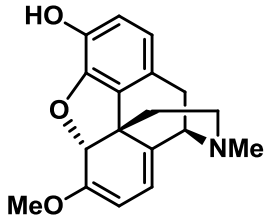

**75**: $R_f$ = 0.35 [hexane/EtOAc (1:1)]; mp 145 °C (EtOAc); $[\alpha]_D^{20}$ = –199.2° (*c* = 0.25, MeOH); IR (neat) *v* 3189, 2936, 2803, 2235, 2069, 1455, 1154, 1102, 1028, 943, 905, 757 $cm^{-1}$; $^1H$ NMR (600 MHz, MeOH-$d_4$) $\delta$ 6.53 (d, *J* = 8.1 Hz, 1H), 6.48 (d, *J* = 8.1 Hz, 1H), 6.02-5.95 (m, 2H), 4.83 (s, 1H), 4.15 (s, 1H), 3.62 (s, 3H), 3.42 (d, *J* = 6.6 Hz, 1H), 3.26 (d, *J* = 18.5 Hz, 1H), 2.87 (td, *J* = 12.7, 5.5 Hz, 1H), 2.64 (dd, *J* = 12.2, 5.2 Hz, 1H), 2.56 (dd, *J* = 18.5, 6.7 Hz, 1H), 2.46 (td, *J* = 12.3, 3.7 Hz, 1H), 2.37 (s, 3H), 1.81 (dd, *J* = 13.0, 2.8 Hz, 1H); $^{13}C$ NMR (151 MHz, MeOH-$d_4$) $\delta$ 146.9, 140.2, 139.5, 134.1, 126.8, 124.4, 121.2, 118.9, 118.5, 92.7, 81.2, 61.2, 54.0, 53.7, 51. 6, 49.9, 46.9, 43.5, 35.4, 33.7, 24.0; MS (EI+, *m/z* (rel.%)): 368 (10), 297 (40), 241 (15), 184 (40); HRMS (ESI) Anal. Calcd. for $C_{20}H_{20}N_2O_3S$: 368.12, found 368.11.

**(–)-(4*R*,4a*S*,7*S*,7a*R*,12b*S*,14*R*)-9-Hydroxy-7-methoxy-3-methyl-1,2,3,4,7,7a-hexahydro-4a,7-(epithiomethano)-4,12-methanobenzofuro[3,2-e]isoquinoline-14-carbonitrile (76)**.




**76**: $R_f$ = 0.23 [hexane/EtOAc (1:1)]; mp 170-174 °C (EtOAc); $[\alpha]_D^{20}$ = –1.16° (*c* = 0.5, MeOH); IR (neat) *v* 3509, 3358, 2926, 2803, 2241, 1638, 1497, 1112, 1030, 891, 761 $cm^{-1}$; $^1H$ NMR (600 MHz, DMSO-$d_6$) $\delta$ 6.49 (d, *J* = 8.0 Hz, 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 6.03 (d, *J* = 8.9 Hz, 1H), 5.74 (d, *J* = 8.7 Hz, 1H), 4.94 (s, 1H), 4.73 (s, 1H), 3.51 (s, 3H), 3.43 (d, *J* = 6.4 Hz, 1H), 3.10 (d, *J* = 18.4 Hz, 1H), 2.65 (td, *J* = 12.7, 5.4 Hz, 1H), 2.57-2.45 (m, 8H), 2.27 (s, 3H), 2.26-2.20 (m, 1H), 1.63 (dd, *J* = 12.9, 2.6 Hz, 1H); $^{13}C$ NMR (151 MHz, DMSO-$d_6$) $\delta$ 145.2, 138.9, 136.5, 132.9, 126.8, 124.8, 119.9, 118.7, 117.1, 87.1, 79.9, 59.2, 52.5, 51.4, 50.1, 45.2, 42.8, 33.6, 32.2, 22.5; MS (EI+, *m/z* (rel.%)): 362 (10), 297 (20), 78 (90), 63 (100); HRMS (ESI) Anal. Calcd. for $C_{20}H_{20}N_2O_3S$: 368.1195, found 368.1195.

**(–)-Oripavine 2**.




Method **E**: To a solution of **75** (400 mg, 1.09 mmol) in DMSO (1.5 mL) was added 2,6-di-*tert*-butyl-4-methylphenol (BHT) (21 mg, 0.109 mmol) and 2,3-dimethylbutadiene (2.5 mL, 22.1 mmol), which was then charged to a sealed tube. The reaction was stirred vigorously for 24 h at 75 °C. The 2,3-dimethylbutadiene was removed by under reduced pressure and the residue dissolved $CHCl_3$ (20 mL). The organic solution was washed with $H_2O$ (5 mL), then concentrated under reduced pressure. The residue was purified by column chromatography [$CH_2Cl_2$/MeOH (9:1)] to yield oripavine **2** (210 mg, 65%). NMR spectra, $R_f$, and mp, were in agreement with previously published data.[68]

Method **F**: To a solution of **76** (66 mg, 0.18 mmol) in $CH_2Cl_2$ (2 mL) was added *m*CPBA 77% (40 mg, 0.18 mmol) at room temperature for 18 h. The solvent was evaporated under reduced pressure and the solid was then dissolved in EtOH (20 mL) and then heated to reflux for 2.5 h. The solvent was evaporated under reduced pressure and the crude residue purified by column chromatography [$CHCl_3$/MeOH (4:1)] to yield oripavine **2** (42 mg, 78%).

**2**: $R_f$ = 0.25 [$CHCl_3$/MeOH (4:1)]; $[\alpha]_D^{20}$ = –215.2° (*c* = 3.5, $CHCl_3$), [lit.[68] $[\alpha]_D^{20}$ = –216.9° (*c* = 3.44, $CHCl_3$)]; mp 200-201 °C (MeOH), lit.[68] mp 201-203 °C (EtOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.65 (d, *J* = 8.1 Hz, 1 H), 6.55 (d, *J* = 8.1 Hz, 1 H), 5.57 (d, *J* = 6.4 Hz, 1 H), 5.30 (s, 1 H), 5.07 (d, *J* = 6.4 Hz, 1 H), 3.82-3.50 (m, 4 H), 3.31 (d, *J* = 18.0 Hz, 1 H), 2.87 (t, *J* = 11.2 Hz, 1 H), 2.79-2.58 (m, 2 H), 2.47 (s, 3 H), 2.23 (td, *J* = 12.7, 5.2 Hz, 1 H), 1.74 (d, *J* = 12.2 Hz, 1 H). The NMR spectra matched previously published data.

**Direct conversion of thebaine to oripavine**:

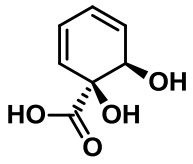
Thebaine (250 mg, 0.8 mmol), $CaCl_2 \cdot 2H_2O$ (146 mg, 1.0 mmol), and **71** (175 mg, 1.0 mmol), were dispersed in $C_6H_6$ (4.5 mL) and methanol (5.5 mL). A large stirring bar is necessary to prevent seizing. The mixture was stirred for 5 min, then $NEt_3$ (0.14 mL, 1.0 mmol) was added drop-wise over 90 min at room temperature. Slow addition of base is necessary to prevent thioaldehyde polymerization. The off-white solution/suspension began to turn yellowish with more base added. The reaction mixture was stirred at 400 rpms for 18 h with no special exclusion of moisture or atmosphere. The reaction was diluted with EtOAc (15 mL), then filtered through a plug of sand and Celite. The organic solvents were then removed under reduced pressure, and the orange solid residue as a mixture of isomers **72**, **73**, and **74**, was carried on to the next step without further purification.

The mixture of the isomeric adducts were dissolved in $CH_2Cl_2$ (10 mL) and cooled to 0 °C. $BBr_3$ (0.77 mL, 8.0 mmol) was then added in a single portion. The transparent orange solution immediately turned an opaque brown. The reaction was allowed to progress for 20 min. The reaction was quenched by the addition of ice-cold water (1 mL), then slowly, ice-cold 10% NaOH solution (10 mL) was added. The slightly basic biphasic solution was then filtered through a short plug of sand and silica to remove boron and bromide byproducts. The reaction vessel was washed with [$CHCl_3$/*i*PrOH (9:1)] (2 x 15 mL). The orange transparent filtrate was washed with brine (5 mL), dried over $MgSO_4$, and then concentrated under reduced pressure to provide a mixture of 3-O-demethylated isomers (213 mg, 72% for 2 steps). Note: the 3-O-demethylated compound arising from **72**, was never characterized, merely observed by TLC.

The mixture of dihydrothiopyran adducts **75** and **76** (200 mg, 0.54 mmol) of oripavine were dissolved in [*i*PrOH/DMSO (8:1)] (2.25 mL), then transferred to a sealed tube. 2,3-Dimethylbutadiene (1.8 mL, 16.2 mmol) was added under argon, then the tube was sealed and heated to 80 °C behind an explosion-proof shield for 20 h. The completion of the reaction was confirmed by TLC and HPLC-MS, as oripavine appeared as the major product. The volatiles were removed under reduced pressure, then crude mixture was then purified by flash column chromatography [$CHCl_3$/MeOH (4:1)] to provide oripavine **2** (105 mg, 65%, 44%

overall yield for three steps). NMR spectra, $R_f$, and mp, were in agreement with previously published data.[68]

**Sodium (–)-(1*S*,6*R*)-1,6-Dihydroxycyclohexa-2,4-dienecarboxylate (4).**




The whole-cell biotransformation of benzoic acid was performed based on a modified procedure established by Mihovilovic and co-workers.[69] Lysogeny broth (LB)(II) medium (100 mL) was inoculated with a single colony of *Ralstonia eutrophus* B9 that was grown on LB(II) agar plates at 30 °C for two days. The inoculated medium was incubated at 30 °C on an orbital shaker at 185 RPM until $OD_{256}$ = 4.8 (1:10 dilution; 24 h). The cellular suspension (80 mL) was used as a pre-culture and added to a 15 L Sartorius Biostat C bioreactor that contained Hutner's Mineral Base (HMB) medium (8.4 L) at pH = 7.4, aerated with sterile air at 3 L $min^{-1}$, agitation speed of 300 RPM, and D-fructose (50 mL of a 1.5 M aqueous solution) concentration of 0.009 M. The culture was grown until an $OD_{256}$ = 2.8 (1:10) was achieved (20 h), and then induced with sodium benzoate (12 mL of a 1.5 M aqueous solution; 18 mmol) and D-fructose (53 mL of a 1.5 M aqueous solution; 80 mmol). After 6 h, consumption of benzoate was observed

by UV analysis (265 nm) and a repetitive feeding program was initiated at which 15 min feeding of an aqueous solution of sodium benzoate (22 mL, 1.5 M; 1.5 mL/min feed rate) and aqueous D-fructose (22 mL, 1.5 M; 1.5 mL/min feed rate) was performed every 3 h over the course of 4 d; a total of 170 g of sodium benzoate was fed. After the feeding regime was completed the broth was drained and separated from cell matter by centrifugation at 5 °C (10,000 RPM). The dark brown ferment broth was concentrated by rotary evaporation at 45 °C to provide the *ipso* diene diol carboxylate as the mixed potassium/sodium salt. NMR spectroscopy assay was used to establish a weight-weight percentage of the crude material with an internal standard (potassium benzoate). A total mass of 240 g of crude material was obtained and corresponded to 162 g of the salt of *ipso* diol **4** that could be stored at room temperature.

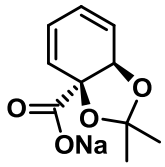
**HMB Media for 8 L Fermentation:**

KOH (3.2 g), nitriloacetic acid (1.6 g), $MgSO_4 \cdot 7H_2O$ (4.64 g), $CaCl_2 \cdot 2H_2O$ (536 mg), $(NH_4)_2SO_4$ (8 g), $(NH_4)_2MoO_4 \cdot 4H_2O$ (1.6 mg), $FeSO_4 \cdot 7H_2O$ (8 mg), $KH_2PO_4$ (21.76 g), $Na_2HPO_4$ (25.84 g) diluted in 8 L of distilled water.

Hutner's Metal Solution (8 mL): $H_2SO_4$ (100 µL), EDTA (0.5 g), $ZnSO_4 \cdot 7H_2O$ (2.2 g), $FeSO_4 \cdot 7H_2O$ (1 g), CuCl (340 mg), $Co(NO_3)_2 \cdot 6H_2O$ (50 mg), $Na_2B_4O_7 \cdot 10H_2O$ (36 mg) diluted in 100 mL of distilled water.

**4**: $R_f$ = 0.20 [EtOAc/MeOH (4:1)]; mp 201-203 °C ($H_2O$; decomposition); $[\alpha]_D^{20}$ = –97.3° (*c* = 1.0, $H_2O$) [lit.[22] $[\alpha]_D^{20}$ = –123.8° (*c* = 1.78, $H_2O$)]; IR (neat) *v* 3392, 3243, 3037, 2884, 1591, 1408, 1394, 1007, 783, 686 $cm^{-1}$; $^1H$ NMR (300 MHz, $D_2O$) $\delta$ 6.03 (dd, *J* = 9.5, 5.2 Hz, 1H), 5.93-5.81 (m, 1H), 5.71-5.64 (m, 2H), 4.77 (s, 1H); $^{13}C$ NMR (75 MHz, $D_2O$) $\delta$ 180.7, 131.0, 127.1, 126.1, 132.2, 75.1, 71.4.

**Sodium (–)-(3a*S*,7a*R*)-2,2-Dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxole-3a-carboxylate (80).**

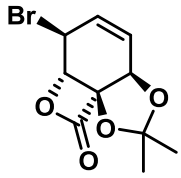



To a slurry of mixed potassium/sodium carboxylate **4** (68 g (101 g at 67% purity), 0.367 mol) in 2,2-DMP (900 mL, 0.4 M) at 0 °C with vigorous stirring was added TFA (168 mL, 2.2 mol) drop-wise over several minutes while the internal temperature was monitored. The reaction mixture was warmed up to room temperature and stirred until the consumption of **4** was observed by TLC. The reaction mixture was filtered over a bed of diatomaceous earth and the filtrate was concentrated under reduced pressure to a dark brown oil. The crude mixture was dispersed in water (100 mL), and extracted with $CH_2Cl_2$ (2 x 300 mL). The organic phases were then extracted with a saturated aqueous $NaHCO_3$

solution (3 x 500 mL) and then concentrated to dryness under reduced pressure. The inorganic-salt-contaminated carboxylate was then dissolved in MeOH and the heterogeneous mixture was filtered. The filtrate was concentrated under reduced pressure to yield an off-white solid (55 g, 0.3 mol, 81% yield) of acetonide **80**.

**80**: $R_f$ = 0.9 [EtOAc/MeOH (4:1)]; mp 87-91°C (MeOH) [no known literature value]; $[\alpha]_D^{20}$ = –218.2° (*c* = 1.0, MeOH) [no known literature value]; IR (neat) *v* 3434, 2988, 1680, 1603, 1386, 1207, 1133, 1029, 802, 722 $cm^{-1}$; $^1H$ NMR (300 MHz, $D_2O$) $\delta$ 6.13 (dd, *J* = 9.5, 5.6 Hz, 1H), 6.06 (dd, *J* = 9.6, 5.5 Hz, 1H), 5.92 (dd, *J* = 9.5, 4.3 Hz, 1H), 5.71 (dd, *J* = 9.9, 4.5 Hz, 1H), 4.80 (d, *J* = 4.2 Hz, 1H), 1.43 (s, 3H), 1.33 (s, 3H).

**(+)-(3a*R*,5a*S*,6*S*,8a*R*)-6-Bromo-2,2-dimethyl-5a,6-dihydrooxeto[3',2':1,6]benzo[1,2-*d*][1,3]dioxol-4(8a*H*)-one (81)**.




Small scale:

Acetonide **80** was dissolved in ice cold HCl 6 M (50 mL), then extracted with EtOAc (2 x 30 mL), dried over $Na_2SO_4$, then concentrated under reduced pressure

to provide the carboxylic acid (360 mg, 1.8 mmol). The acid was dissolved in [$CH_2Cl_2$/toluene (30:1)] (31 mL), then NBS (640 mg, 3.6 mmol) was added. The reaction was complete within 3 h at room temperature. The reaction mixture was concentrated under reduced pressure, then adsorbed onto silica. The material was then purified by flash column chromatography [hexane/EtOAc (4:1)]. The pure fraction contents crystallized in white spirals (167 mg, 1.5 mmol, 85%).

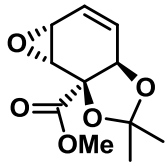
Large scale:

Diene **80** (15 g, 76.5 mmol) was dissolved in $H_2O$ (100 mL). Saturated $NaHCO_3$ (100 mL) was then added, followed by $CH_2Cl_2$ (100 mL). This biphasic mixture was cooled to 0 °C and then $Br_2$ (4 mL, 76.5 mmol) in $CH_2Cl_2$ (30 mL) was added drop-wise over 45 min. The reaction was quenched by the addition of saturated $NaHSO_3$ (50 mL) to ensure the disappearance of red color. The phases were separated and the $CH_2Cl_2$ layer collected. The aqueous layer was extracted with $CH_2Cl_2$ (2 x 150 mL). The combined organic layers were washed with brine, then dried over $Na_2SO_4$, concentrated under reduced pressure to provide a white precipitate. The residue was crystallized from $CH_2Cl_2/Et_2O$ at –20 °C (9.45 g, 34.43 mmol, 45% yield), as white needles.

**81**: $R_f$ = 0.80 [hexane/EtOAc (2:1)]; mp 136-141 °C ($CH_2Cl_2$) [lit.[53] mp 137-142 °C (not reported)]; $[\alpha]_D^{20}$ = +300.7° (*c* = 0.5, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 6.37

(dd, *J* = 10.0, 4.5 Hz, 1H), 6.23-6.03 (m, 1H), 4.92 (d, *J* = 4.4 Hz, 1H), 4.78 (d, *J* = 3.5 Hz, 1H), 4.63 (t, *J* = 4.0 Hz, 1H), 1.55 (s, 3H), 1.44 (s, 3H); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 168.5, 134.0, 122.9, 112.9, 87.3, 78.2, 77.2, 77.0, 76.8, 73.2, 40.3, 27.3, 26.2.

**(–)-(3a*R*,5a*R*,6a*R*,6b*R*)-Methyl 2,2-dimethyl-3a,5a,6a,6b-tetrahydrooxireno[2',3':3,4]benzo[1,2-*d*][1,3]dioxole-6b-carboxylate (82).**




Anhydrous MeOH (80 mL) was charged to a flame-dried 250 mL round bottom flask, then cooled to 0 °C. Sodium metal (3 g, 0.132 mol) was then added portion-wise, a slight exotherm was observed (vigorous evolution of $H_2$, be ready to vent). When no solid sodium pieces remained, the β-lactone **81** (28 g, 0.102 mol) was added in a single portion. The reaction mixture was stirred at room temperature for 18 h. The reaction was quenched by the addition of saturated $NH_4Cl$ solution, MeOH was evaporated under reduced pressure, then extracted with EtOAc (5 x 20 mL). The organic extracts were washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure to provide a reddish-brown syrup weighing 25 g. The crude mass was adsorbed onto 50 g 10%

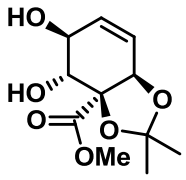
deactivated silica, then purified by suction chromatography to provide a yellowish white solid (18.2 g, 80.5 mmol, 79% yield).

**82**: $R_f$ = 0.35 [hexane/EtOAc (4:1)]; mp 60-61 °C (EtOAc) [lit.[53] mp 55-59 °C (EtOAc)]; $[\alpha]_D^{20}$ = –103.4° (*c* = 1.0, $CHCl_3$); IR (neat) *v* 2994, 1741, 1374, 1249, 1034, 853, 552 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) *δ* 6.14 (ddd, *J* = 10.1, 3.9, 1.7 Hz, 1H), 5.98-5.92 (m, 1H), 5.05-4.91 (m, 1H), 3.89 (s, 3H), 3.69 (d, *J* = 3.6 Hz, 1H), 3.43 (td, *J* = 3.8, 0.9 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H); $^{13}C$ NMR (151 MHz, $CDCl_3$) *δ* 171.9, 133.0, 123.7, 113.2, 80.6, 77.4, 77.2, 77.0, 73.4, 53.4, 51.7, 47.3, 28.4, 27.4.

**Tris(trifluoromethanesulfonate)bismuth(III); $Bi(OTf)_3$** was prepared according to a published protocol.[70] $Bi_2O_3$ (0.5 g, 1.07 mmol) was suspended in [$EtOH/H_2O$ (3:1)] (7.5 mL). TfOH (0.57 mL, 6.44 mmol) was added at once with stirring. The reaction medium was heated to <65 °C for 3 h. The white cloudy mixture was concentrated by lyophilization to provide a free-flowing white powder (1.3 g, 1.9 mmol, 93% yield).

IR (neat) *v* 3360, 1641, 1221, 1182, 1032, 629, 518 $cm^{-1}$.

**(+)-(3a*S*,4*R*,5*S*,7a*R*)-Methyl 4,5-dihydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-3a-carboxylate (83).**

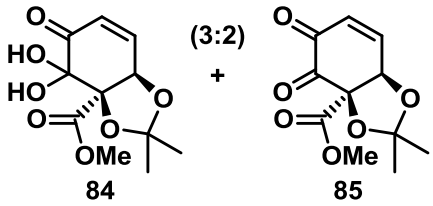



To the vinyl epoxide **82** (150 mg, 0.66 mmol) was added $Bi(OTf)_3$ (44 mg, 0.066 mmol), then [MeCN/$H_2O$ (4:1)] (1.5 mL). The reaction mixture was aged for 2 h at room temperature. TLC (visualized by CAM stain) indicated consumption of starting material, and was thus concentrated under reduced pressure to a yellow oil with solid bismuth salt suspension. The residue was then dispersed in EtOAc and filtered through a short plug of sand and diatomaceous earth. The filtrate was then concentrated under reduced pressure. The diol was then purified by column chromatography [hexanes/EtOAc (1:4)] to provide a sticky, viscous, colorless, clear oil, with an odor of fresh soil, which solidified upon standing over 3 d (115 mg, 0.47 mmol, 72% yield).

**83**: $R_f$ = 0.55 (EtOAc); mp 81-84 °C (EtOAc); $[\alpha]_D^{20}$ = +38.0 (*c* = 2.85, MeOH); IR (neat) *v* 3451, 2989, 1729, 1380, 1209, 1037, 876 $cm^{-1}$; $^1H$ NMR (600 MHz, DMSO-$d_6$) $\delta$ 5.77 (d, *J* = 10.3 Hz, 1H), 5.69 (dd, *J* = 10.2, 2.0 Hz, 1H), 5.52 (d, *J* = 4.5 Hz, 1H), 5.08 (d, *J* = 6.1 Hz, 1H), 4.56 (s, 1H), 4.14 (s, 1H), 3.64 (s, 3H), 3.37 (dd, *J* = 7.9, 4.6 Hz, 1H), 1.41 (s, 3H), 1.29 (s, 3H); $^{13}C$ NMR (151 MHz, DMSO-$d_6$) $\delta$ 171.4, 135.6, 122.0, 110.5, 85.6, 76.2, 75.1, 69.1, 52.0, 40.1, 40.0, 39.8, 39.7, 39.7, 39.6, 39.4, 39.3, 27.9, 26.0, 25.1; MS (EI) *m/z* (%) 240 (20), 229 (55), 199

(100). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found C, 54.31; H, 6.62. The stereochemistry of the vicinal diol were established by COSY, HSQC, and NOESY.

**(3a*R*,7a*R*)-Methyl 4,4-Dihydroxy-2,2-dimethyl-5-oxo-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-3a-carboxylate (84/85).**

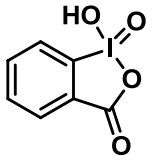



To the *trans*-diol **83**, (80 mg, 0.328 mmol) was added $MnO_2$ (570 mg, 6.55 mmol) and EtOAc (10 mL). The mixture was vigorously stirred under argon for 10 days. The product was purified by filtration through Celite and subsequent adsorption to silica, then by chromatography [hexane/EtOAc (1:1)] to provide a yellow oil (65 mg, 0.271 mmol, 83% yield).

**84**/**85**: $R_f$ = 0.65 [hexane/EtOAc (1:1)]; $[\alpha]_D^{20}$ = a sample of high enough purity could not be attained; IR (neat) *v* 3442, 2992, 1713, 1382, 1266, 1119, 1041 $cm^{-1}$; $^1$H NMR (600 MHz, Acetone-$d_6$) $\delta$ 7.34 (dd, *J* = 10.5, 4.1 Hz, 1H), 6.94 (dt, *J* = 29.3, 14.6 Hz, 2H), 6.66 (d, *J* = 10.5 Hz, 1H), 6.25 (t, *J* = 11.7 Hz, 2H), 5.73 (s, 2H), 5.44 (d, *J* = 4.1 Hz, 1H), 5.32 (s, 1H), 5.10 (d, *J* = 3.6 Hz, 2H), 3.83 (s, 3H), 3.72 (s, 5H), 1.51 (s, 3H), 1.50 (s, 5H), 1.47 (s, 3H), 1.41 (s, 5H); $^{13}$C NMR (151 MHz,

Acetone-$d_6$) $\delta$ 192.5, 188.6, 181.7, 169.9, 167.3, 146.4, 143.5, 132.2, 126.6, 114.5, 112.9, 90.5, 87.7, 86.6, 77.9, 75.2, 52.9, 51.7, 26.8, 26.5, 25.7, 25.1; MS (EI) *m/z* (%) 229 (15), 159 (30), 109 (37), 95 (100); The proton and carbon data correspond to the mixture of α-diketone and its hydrate. The compound could not be purified to give clean HRMS data, and therefore it was never sent out for combustion analysis.

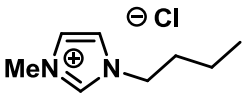
**2-Iodoxybenzoic acid (IBX).**




Prepared according to a published protocol.[71] A three-neck round bottom flask equipped with stir bar and condenser was charged with $KBrO_3$ (5.5 g, 33 mmol) and aqueous $H_2SO_4$ (44 mL, 0.5 M). The vessel was heated to 60 °C, and when all solids were dissolved, *o*-iodobenzoic acid (5.5 g, 22 mmol) was added portion-wise over about 30 min. The reaction mixture turned orange and bromine vapor was evolved though the condenser and trapped by bubbling through a solution of saturated aqueous $Na_2S_2O_3$. After about 2.5 h, the reaction vessel was cooled by ice bath and then the solids were collected by filtration. The filter cake was washed with ice-cold water (30 mL), EtOH (2 x 5 mL), then again with ice-cold

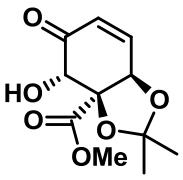
water (30 mL). The sticky white solid was dried under reduced pressure, then stored at –20 °C (5.3 g, 20 mmol, 91% yield).

**1-Butyl-3-methyl-1H-imidazol-3-ium chloride ([bmim]Cl).**




Prepared according to a published protocol.[72] A round bottom flask equipped with stir bar and condenser was charged with 1-methyl imidazole (9.7 mL, 121 mmol), *n*-butyl chloride (14 mL, 134 mmol), and toluene (12 mL), then heated to reflux for 20 h. The reaction mixture concentrated under reduced pressure to provide a viscous, odorless, amber liquid (21.1 g, 120.8 mmol, 99% yield). **[Bmim]Cl**: IR (neat) *v* 3377, 2985, 1566, 1462, 1168, 623 $cm^{-1}$; $^{1}H$ NMR (400 MHz, CDCl3) $\delta$ 10.93 (d, *J* = 7.2 Hz, 1H), 7.39 (s, 1H), 7.29 (s, 1H), 4.31 (t, *J* = 7.4 Hz, 2H), 4.12 (s, 3H), 1.94-1.83 (m, 2H), 1.44-1.31 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

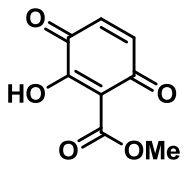
**(+)-(3a*S*,4*S*,7a*R*)-Methyl 4-hydroxy-2,2-dimethyl-5-oxo-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-3a-carboxylate (86).**



[Bmim]Cl (1.5 mL) and water (0.3 mL) were mixed at room temperature in a flask open to atmosphere. IBX (154 mg, 0.55 mmol) was added, which dissolved over about 5 min. The *trans*-diol **83** (131 mg, 0.537 mmol) was then added in one portion and stirred for 3 h at room temperature. When the reaction was complete, the product was extracted with EtOAc (5 x 3 mL). The product was purified by flash column chromatography, to provide **86** as a white solid (105 mg, 0.433 mmol, 80%)

**86**: $R_f$ = 0.42 [hexane/EtOAc (1:1)]; $[\alpha]_D^{20}$ = +2.4 (*c* = 0.8, $CHCl_3$); mp 101-103 °C (EtOAc); IR (neat) *v* 3664, 2978, 2889, 1385, 1259, 1154, 967, 876 $cm^{-1}$; $^1H$ NMR (600 MHz, DMSO-$d_6$) $\delta$ 6.94 (dd, *J* = 10.2, 4.0 Hz, 1H), 6.20 (dd, *J* = 10.2, 0.7 Hz, 1H), 6.02 (d, *J* = 4.9 Hz, 1H), 5.02 (dd, *J* = 4.1, 0.6 Hz, 1H), 4.26 (d, *J* = 4.8 Hz, 1H), 3.66 (s, 3H), 1.49 (s, 3H), 1.40 (s, 3H); $^{13}C$ NMR (151 MHz, DMSO-$d_6$) $\delta$ 195.5, 169.7, 140.2, 128.9, 111.3, 85.9, 75.0, 73.4, 52.4, 27.4, 25.5; MS (EI) *m/z* (%) 220 (5), 205 (27), 149 (8), 105 (27), 85 (65), 83 (100), 72 (100); Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83; Found C, 54.39; H, 5.67.

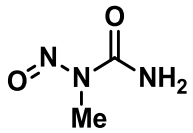
**Methyl 2-Hydroxy-3,6-dioxocyclohexa-1,4-dienecarboxylate (88).**



The ketol **86** (30 mg, 0.124 mmol) was dissolved in THF (0.6 mL, 0.2 M), then TMSCl (17.2 µL, 0.136 mmol), and then slowly $NEt_3$ (19 µL, 0.136 mmol). The reaction mixture went from transparent to cloudy and TLC [hexane/EtOAc (2:1)] indicated full conversion to the silyl ether. DBU (30.5 µL, 0.248 mmol) was added slowly. The reaction mixture quickly turned to a dark red and a black precipitate formed. After 2 min, saturated $NaHCO_3$ (2 mL) was added, followed by EtOAc (4 mL). The material was then purified by flash chromatography [hexane/EtOAc (2:1)] to give a white solid (20 mg, 0.1098 mmol, 88% yield).

**88**: $R_f$ = 0.55 [hexane/EtOAc (1:1)]; mp 135-137 °C ($CHCl_3$); IR (neat) *v* 3410, 1675, 1459, 1320, 1161, 1123, 790 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.09 (d, *J* = 8.9 Hz, 1H), 6.45 (d, *J* = 8.8 Hz, 1H), 5.20 (s, 1H), 4.12 (s, 3H); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 169.8, 152.9, 137.5, 122.2, 107.3, 99.9, 53.1, 29.7; MS (EI) *m/z* (%) 184 (45), 152 (100), 124 (40), 96 (20), 69 (15). Spectroscopic evidence for this compound has been somewhat contradictory, and it remains unclear exactly what the oxidation state of the aromatic ring is. Because this compound was a dead-end product it was not submitted for combustion analysis.

**1-Methyl-1-nitrosourea (MNU).**

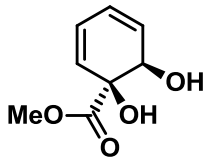



Prepared according to a published protocol.[73] Ice-cold methylamine 40% aq (130 mL, 1.5 mol) was placed in a 1 L round bottom flask equipped with addition funnel. Concentrated HCl (155 mL, 12 M) was poured into water (200 mL) then added slowly over 30 min to the methylamine solution. Urea (300 g, 5 mol) was added over several minutes with warming to the reaction solution. With the addition complete, the mixture was heated to reflux for 2 h (~150 °C) then allowed to cool to room temperature. $NaNO_2$ (114 g, 1.65 mol) was added directly to the reaction mixture and stirred until it was a viscous transparent yellow solution.

To a 5 L 3-neck round bottom flask equipped with a mechanical stirrer was added ice (600 g) and $H_2SO_4$ (53.5 mL, 1 mol), which was then cooled to <0 °C by a brine-ice bath. To this mixture was slowly added the nitrite/methylurea solution over about 1 h by addition funnel, keeping the internal reaction mixture temperature <5 °C. The precipitate was then collected by filtration, and the cake was washed with ice-cold water (50 mL) and then dried in a vacuum desiccator.

The dried light yellowish/orange white solid (127 g, 1.5 mol) was stored at –20 °C. Please consult the MSDS of MNU, it is a very strong carcinogen.

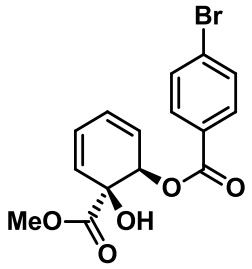
**(–)-(1*S*,6*R*)-Methyl 1,6-Dihydroxycyclohexa-2,4-dienecarboxylate (55).**




To a solution of *ipso* diol **4** (4.0 g, 25.6 mmol) in THF (32 mL, 0.8 M) at 0 °C was added diazomethane (excess) in $Et_2O$ drop-wise over 30 min.[74] The reaction mixture was allowed to warm to room temperature. After warming to ambient temperature the reaction mixture was titrated with AcOH (bubbling cessation) and then concentrated under reduced pressure to provide an orange oil. The crude mass was purified by column chromatography to provide a white solid (3.26 g, 19.2 mmol, 75% yield).

**55**: *Rf* = 0.23 [hexane/EtOAc (1:1)]; mp 59-60 °C ($Et_2O$) [lit.[29] mp 59-60 °C ($Et_2O$)]; $[\alpha]_D^{20}$ = –94.2° (*c* = 1.0, $CHCl_3$) [lit.[29] $[\alpha]_D^{20}$ = –96.696° (*c* = 1.0, $CHCl_3$)]; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.08 (dd, *J* = 9.5, 5.1 Hz, 1H), 5.95-5.84 (m, 1H), 5.82-5.68 (m, 2H), 4.79 (d, *J* = 5.1 Hz, 1H), 3.84 (s, 1H), 3.81 (s, 3H), 3.39-3.23 (m, 1H).

**(–)-(1*R*,6*S*)-6-Hydroxy-6-(methoxycarbonyl)cyclohexa-2,4-dien-1-yl 4-bromobenzoate (90).**

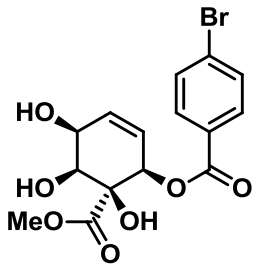



The diene-diol **55** (1.2 g, 7.06 mmol) was dissolved in $CH_2Cl_2$ (30 mL, 0.24 M), then TMEDA (1.05 mL, 7.06 mmol) was added. The mixture was cooled to –78 °C, then 4-bromo-benzoylchloride (1.56 g, 7.13 mmol) in $CH_2Cl_2$ (5 mL) was added drop-wise. After a few minutes the transparent yellow solution became white and opaque. The reaction was allowed to progress for an additional 3 h, then quenched by the addition of saturated $NaHCO_3$ (10 mL). The organic layer was collected, and the aqueous was extracted an additional time with $CH_2Cl_2$ (30 mL). The combined organic layers were dried over $Na_2SO_4$. The concentrated residue was purified by column chromatography gradient elution [hexane/EtOAc (9:1 to 4:1)] to provide clear oil (2.1 g, 5.93 mmol, 84% yield).

**90**: $R_f$ = 0.75 [hexane/EtOAc (1:1)]; $[\alpha]_D^{20}$ = –112.1° (*c* = 0.5, $CHCl_3$); IR (neat) *v* 3483, 2953, 1718, 1588, 1256 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.95-7.88 (m, 2H), 7.61-7.54 (m, 2H), 6.28-6.19 (m, 1H), 6.19-6.07 (m, 2H), 5.88-5.78 (m, 2H), 3.84 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) *δ* 174.8, 165.2,

131.9, 131.4, 128.7, 128.2, 126.7, 126.5, 125.0, 124.1, 73.3, 73.1, 53.8; MS (EI) *m/z* (%) 249 (7), 201 (10), 182 (30), 152 (57), 120 (100); HRMS (EI) calcd for $C_{15}H_{13}BrO_5$: 351.9946. Found 351.9935; Anal. Calcd for $C_{15}H_{13}BrO_5$: C, 51.07; H, 3.71. Found C, 50.73; H, 3.74.

**(–)-(1*R*,4*S*,5*S*,6*S*)-4,5,6-Trihydroxy-6-(methoxycarbonyl)cyclohex-2-en-1-yl 4-bromobenzoate (91).**

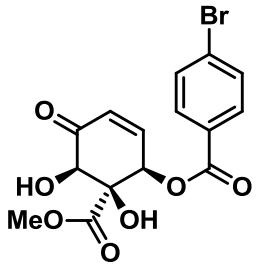



The allylic alcohol **90** (335 mg, 0.949 mmol) was dissolved in $CH_2Cl_2$ (95 mL, 0.01 M), then TMEDA (199 µL, 1.33 mmol) was added. The solution was cooled to –78 °C and then $OsO_4$ (250 mg, 0.983 mmol) in $CH_2Cl_2$ (1.5 mL) was added slowly to the reaction mixture. The clear solution turned a dark red upon complete addition of the osmium. After 1 h TLC indicated complete consumption of the starting material, so the $CH_2Cl_2$ was removed under reduced pressure. The residue was dissolved in THF (10 mL) and to this solution was added saturated $NaHSO_3$ (10 mL). The mixture was then heated to reflux for 3 h. The solvents were removed under reduced pressure to provide a grey powder, which was

suspended in MeOH (40 mL) and subsequently filtered through a tightly packed, thin bed of Celite. The slightly yellow filtrate was concentrated under reduced pressure to provide a milky white residue which began to crystallize on standing. The residue was purified anyway by flash column chromatography [hexane/EtOAc (2:1 to 1:1 to 1:2)] to provide a glistening white foam (340 mg, 0.883 mmol, 93% yield).

**91**: $R_f$ = 0.20 [hexane/EtOAc (1:2)]; mp 49-51 °C (EtOAc); $[\alpha]_D^{20}$ = –251.3° (*c* = 0.3, acetone); IR (neat) *v* 3500, 1720, 1676, 1587, 1261 $cm^{-1}$; $^1H$ NMR (600 MHz, Acetone-$d_6$) $\delta$ 8.04 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 6.25 (d, *J* = 2.1 Hz, 1H), 5.78 (dd, *J* = 10.5, 1.7 Hz, 1H), 5.66 (dt, *J* = 10.5, 1.9 Hz, 1H), 5.19 (s, 1H), 4.56 (dt, *J* = 14.9, 7.4 Hz, 1H), 4.52 (d, *J* = 3.8 Hz, 1H), 4.24 (s, 1H), 4.04 (d, *J* = 8.7 Hz, 1H), 3.69 (s, 3H); $^{13}C$ NMR (151 MHz, Acetone-$d_6$) $\delta$ 172.4, 164.8, 131.7, 131.6, 131.3, 129.4, 127.7, 124.4, 78.4, 73.3, 70.9, 66.0, 51.9; MS (EI) *m/z* (%) 267 (5), 199 (70), 184 (100), 154 (40); HRMS (EI) calcd for $C_{13}H_{12}BrO_5$: 326.9868. Found 326.9979 (loss of methyl carboxylate); Anal. Calcd for $C_{15}H_{15}BrO_7$: C, 46.53; H, 3.90. Found C, 46.30; H, 4.12.

**(–)-(1*R*,5*R*,6*S*)-5,6-Dihydroxy-6-(methoxycarbonyl)-4-oxocyclohex-2-en-1-yl 4-bromobenzoate (92).**

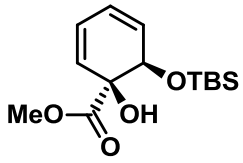



The triol **91** (55 mg, 0.142 mmol) was dissolved in dioxane (7 mL), DDQ (51 mg, 0.227 mmol) was then added at once, and the mixture was heated at 70 °C for 6 days. When the starting material was consumed, dioxane was removed under reduced pressure, then the mixture was dissolved in EtOAc (10 mL). The product was washed with saturated $NaHSO_3$ (5 mL) and saturated $NaHCO_3$ (5 mL) then dried over $MgSO_4$ and filtered through Celite and concentrated under reduced pressure. The orange residue was purified by column chromatography [hexane/EtOAc (2:1 to 1:1 to 1:2)] to provide a white solid (45 mg, 0.117 mmol, 82%).

**92**: $R_f$ = 0.75 [hexane/EtOAc (1:2)]; mp 81-82 °C (EtOAc); $[\alpha]_D^{20}$ = –208.4° (*c* = 0.6, acetone); IR (neat) *v* 3459, 2955, 1697, 1587, 1260, 1094 $cm^{-1}$; $^1H$ NMR (600 MHz, Acetone-$d_6$) $\delta$ 8.06 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 6.91 (dd, *J* = 10.3, 3.3 Hz, 1H), 6.35 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.18 (d, *J* = 10.3 Hz, 1H), 5.51 (s, 1H), 5.28 (d, *J* = 4.7 Hz, 1H), 4.37 (d, *J* = 4.3 Hz, 1H), 3.70 (s, 3H); $^{13}C$ NMR (151

MHz, Acetone-$d_6$) $\delta$ 205.5, 205.3, 205.2, 194.5, 170.7, 165.9, 164.6, 142.8, 131.8, 131.8, 131.7, 131.4, 129.8, 128.9, 128.6, 127.9, 127.3, 79.7, 75.7, 69.8, 52.1; MS (EI) *m/z* (%) 383 (3), 265 (5), 199 (10), 184 (100), 154 (25), 125 (12); HRMS (EI) calcd for $C_{13}H_{10}BrO_5$: 383.9845. Found 383.9835; Anal. Calcd for $C_{15}H_{13}BrO_7$: C, 46.78; H, 3.40. Found C, 46.49; H, 3.47.

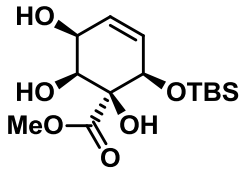
**(–)-(1*S*,6*R*)-Methyl 6-((tert-Butyldimethylsilyl)oxy)-1-hydroxycyclohexa-2,4-dienecarboxylate (93).**




The diene **55** (730 mg, 4.3 mmol) was dissolved in $CH_2Cl_2$ (22 mL) followed by the addition of imidazole (322 mg, 4.3 mmol) and DMF (5 mL). TBSCl (647 mg, 4.3 mmol) was then added at once. The reaction was left to age 20 h. The reaction mixture was diluted with water (50 mL), and the organic layer collected. The aqueous layer was then extracted with $CH_2Cl_2$ (2 x 20 mL). The combined organic extracts were washed with 10% $CuSO_4$ solution (50 mL), followed by brine (50 mL), and then dried over $MgSO_4$. The dry extract was filtered and concentrated under reduced pressure to provide a yellow oil. The oil was purified by gravity chromatography [hexane/EtOAc (5:1)] as a clear oil (500 mg, 1.75 mmol, 41%).

**93**: $R_f$ = 0.25 [hexane/EtOAc (4:1)]; $[\alpha]_D^{20}$ = –36.8° (*c* = 3.0, $CH_2Cl_2$); $^1$H NMR (300 MHz, Acetone-$d_6$) $\delta$ 6.11 (dd, *J* = 9.5, 5.2 Hz, 1H), 5.98-5.85 (m, 1H), 5.79 (dd, *J* = 9.5, 1.0 Hz, 1H), 5.72-5.63 (m, 1H), 4.96 (s, 1H), 3.79 (s, 3H), 3.38 (s, 1H), 0.88 (s, 9H), 0.10 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR (151 MHz, Acetone-$d_6$) $\delta$ 175.2, 131.9, 126.6, 124.8, 122.5, 74.6, 72.7, 52.9, 25.6, 17.9, –4.4, –5.3. NMR data matched that reported by Lewis and co-workers.[28]

**(–)-(1*S*,2*R*,5*S*,6*S*)-Methyl 2-((tert-Butyldimethylsilyl)oxy)-1,5,6-trihydroxycyclohex-3-enecarboxylate (94).**

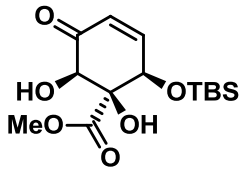



The protected diene **93** (272 mg, 0.956 mmol) was dissolved in $CH_2Cl_2$ (90 mL, 0.01 M) followed by the addition of TMEDA (0.15 mL, 1 mmol). The solution was cooled to –78 °C and then $OsO_4$ (250 mg, 0.983 mmol) in $CH_2Cl_2$ (1.5 mL) was added slowly to the reaction mixture. The clear solution turned a dark red upon complete addition of the osmium. After 1 h TLC indicated complete consumption of the starting material, so the $CH_2Cl_2$ was removed under reduced pressure. The residue was dissolved in THF (10 mL) and to this solution was added saturated $NaHSO_3$ (10 mL). The mixture was then heated to reflux for 3 h. The solvents

were removed under reduced pressure to provide a grey powder, which was suspended in MeOH (50 mL) and subsequently filtered through a tightly packed, thin bed of Celite. The slightly yellow filtrate was concentrated under reduced pressure to provide a milky white residue which began to crystallize on standing. The crude mixture was purified by flash chromatography [hexane/EtOAc (2:1)] to yield (70 mg, 0.231 mmol, 23%).

**94**: $R_f$ = 0.33 [hexane/EtOAc (1:1)] ($KMnO_4$ stain); mp 108-110 °C (EtOAc); $[\alpha]_D^{20}$ = –7.3° (*c* = 0.7, acetone); IR (neat) *v* 3542, 3406, 2953, 2928, 2879, 2856, 1747, 1663 $cm^{-1}$; $^1H$ NMR (300 MHz, Acetone-$d_6$) $\delta$ 5.98 (dd, *J* = 9.8, 4.9 Hz, 1H), 5.67 (d, *J* = 9.8 Hz, 1H), 4.32 (d, *J* = 9.8 Hz, 1H), 4.25 (q, *J* = 4.6 Hz, 1H), 4.19 (d, *J* = 4.6 Hz, 1H), 3.85 (ddd, *J* = 9.8, 7.7, 4.4 Hz, 1H), 3.76 (s, 1H), 3.74 (s, 3H), 3.68 (d, *J* = 7.7 Hz, 1H), 0.89 (s, 9H), 0.18 (s, 3H), 0.07 (s, 3H); $^{13}C$ NMR (75 MHz, Acetone-$d_6$) $\delta$ 173.8, 131.0, 128.5, 76.2, 72.7, 68.9, 66.9, 51.9, 25.5, 18.0, –4.4, –5.8; MS (EI) *m/z* (%) 261 (15), 225 (30), 197 (80), 155 (30), 75 (100); HRMS (EI) calcd for $C_{14}H_{26}O_6Si$: 261.0794. Found 261.0802; Anal. Calcd for: C, 52.80; H, 8.23. Found C, 53.52; H, 8.40.

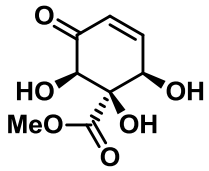
**(–)-(1*S*,2*R*,6*R*)-Methyl 2-((tert-Butyldimethylsilyl)oxy)-1,6-dihydroxy-5-oxocyclohex-3-enecarboxylate (95).**




The allylic triol **94** (20 mg, 66 µmol) was dissolved in dioxane, followed by the addition of DDQ (19.5 mg, 86 µmol). The yellow solution was held at 85 °C for 3 days. The ketol **94** was isolated by preparative TLC (15 mg, 50 µmol, 75%).

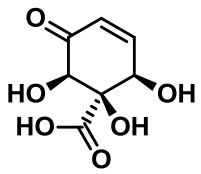
**95**: $R_f$ = 0.75 [hexane/EtOAc (1:1)]; $[\alpha]_D^{20}$ = –12.6° (*c* = 0.5, acetone); IR (neat) *v* 3494, 2955, 2858, 1754, 1693, 1249, 1120, 836cm$^{-1}$; $^1$H NMR (300 MHz, Acetone-$d_6$) $\delta$ 6.90 (d, *J* = 9.9 Hz, 1H), 6.19 (d, *J* = 9.9 Hz, 1 H), 4.56 (s, 1H), 4.39 (d, *J* = 2.6 Hz, 1H), 4.36 (t, *J* = 3.6 Hz, 1H), 4.17 (sext, *J* = 2.6 Hz, 1H), 3.79 (s, 3H), 0.87 (s, 9H), 0.17 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR (75 MHz, Acetone-$d_6$) $\delta$ 198.1, 172.6, 145.0, 128.8, 76.4, 75.5, 74.7, 52.5, 25.4, 17.9, –4.6, –6.1; MS (EI) *m/z* (%) 259 (45), 241 (80), 213 (80), 209 (100), 181 (40), 75 (90); HRMS (EI) calcd for $C_{14}H_{24}O_6Si$: 259.0638. Found 259.0650.

**(+)-(1*R*,2*R*,6*R*)-Methyl 1,2,6-Trihydroxy-5-oxocyclohex-3-enecarboxylate (96).**




The ketol **95** (5 mg, 16 µmol) was dissolved in MeOH (0.5 mL). To this mixture was added AcOH (2 mg, 33 µmol, ~6 drops) and TBAF 1 M in THF (20 µL, 16 µmol, ~5 drops). When starting material was consumed, the mixture was purified by preparative TLC, providing a yellow residue (2 mg, 9.9 µmol, 63%). **96**: $R_f$ = 0.45 [EtOAc/MeOH/$H_2O$ (90:10:5)]; $[\alpha]_D^{20}$ = +5.2° (*c* = 0.1, acetone); IR (neat) *v* 3428, 2958, 1748, 1699, 1262, 1123 $cm^{-1}$; 1H NMR (300 MHz, Acetone-$d_6$) $\delta$ 6.90 (d, *J* = 10.0 Hz, 1H), 6.18 (d, *J* = 10.0 Hz, 1H), 4.81 (d, *J* = 6.1 Hz, 1H), 4.76 (s, 1H), 4.39 (dd, *J* = 10.2, 3.9 Hz, 1H), 4.31 (d, *J* = 4.0 Hz, 1H), 4.05 (dd, *J* = 10.2, 5.9 Hz, 1H), 3.80 (s, 3H); $^{13}$C NMR (151 MHz, Acetone-$d_6$) $\delta$ 197.9, 172.7, 144.6, 128.9, 75.0, 74.7, 74.6, 52.4.

**(+)-(1*R*,2*R*,6*R*)-1,2,6-Trihydroxy-5-oxocyclohex-3-enecarboxylic acid (79).**



The enone triol **96** (2 mg) was dissolved in water (0.3 mL), and $Ba(OH)_2 \cdot 8H_2O$ (5 mg) was added. The mixture was refluxed for 2 h. $NaHSO_4$ was added and the suspension was filtered. The aqueous mixture was extracted with Et2O (5 mL). Both the organic extract and the aqueous mixture were concentrated under reduced pressure. Both residues were purified by preparative TLC [EtOAc/MeOH/$H_2O$ (90:10:5)]. The reaction condition seemed to have decomposed all organic materials present. No compounds were identified.

## 6. References


1. Way, E. L. & Adler, T. K. The biological disposition of morphine and its surrogates: 1. *Bull. World Health Organ.* **25,** 227 (1961).
2. Butora, G. & Hudlicky, T. The Story of Morphine Structure Elucidation: One Hundred Years of Deductive Reasoning. *Org. Synth. Theory Appl.* **4,** 1–51 (1998).
3. Fist, A. J., Byrne, C. J. & Gerlach, W. L. Harvesting poppy capsules of stably reproducing papaver somniferum to produce straw containing thebaine and oripavine in at least 50% by weight of alkaloid mixture formed, chemically extracting thebaine and/or oripavine. (2002). at <http://www.google.com/patents/US6376221>
4. Rinner, U. & Hudlicky, T. Synthesis of morphine alkaloids and derivatives. *Top. Curr. Chem.* **309,** 33–66 (2012).
5. Endoma-Arias, M. A. A., Cox, D. P. & Hudlicky, T. General Method of Synthesis for Naloxone, Naltrexone, Nalbuphone, and Nalbuphine by the Reaction of Grignard Reagents with an Oxazolidine Derived from Oxymorphone. *Adv. Synth. Catal.* **355,** 1869–1873 (2013).
6. Machara, A., Werner, L., Endoma-Arias, M. A., Cox, D. P. & Hudlicky, T. Improved Synthesis of Buprenorphine from Thebaine and/or Oripavine via Palladium-Catalyzed N-Demethylation/Acylation and/or Concomitant O-Demethylation. *Adv. Synth. Catal.* **354,** 613–626 (2012).

7. Fist, A. J., Byrne, C. J. & Gerlach, W. L. Papaver somniferum strain with high concentration of thebaine and oripavine. (2000). at <http://www.google.com/patents/US6067749>
8. Fist, A. J. *Papaver somniferum strain with high concentration of thebaine*. (Google Patents, 2009). at <http://www.google.com/patents/US20090227796>
9. Wang, P. X., Jiang, T., Cantrell, G. L. & Berberich, D. W. *Preparation of oxymorphone from oripavine*. (Google Patents, 2012). at <http://www.google.com/patents/US8217175>
10. Cox, D. P., Zhang, Y., Zhang, W.-C. & James, K. E. Process for preparing oxycodone having reduced levels of 14-hydroxycodeinone. (2011). at <http://www.google.com/patents/US8058439>
11. Halvorsen, H. & Lovli, T. Preparation of oxycodone. (2009). at <http://www.google.com/patents/WO2009004491A2>
12. Coop, A., Janetka, J. W., Lewis, J. W. & Rice, K. C. L-Selectride as a General Reagent for the O-Demethylation and N-Decarbomethoxylation of Opium Alkaloids and Derivatives1. *J. Org. Chem.* **63,** 4392–4396 (1998).
13. Wu, H. *et al.* Position of Coordination of the Lithium Ion Determines the Regioselectivity of Demethylations of 3,4-Dimethoxymorphinans with L-Selectride. *Org. Lett.* **7,** 2531–2534 (2005).
14. Weissman, S. A. & Zewge, D. Recent advances in ether dealkylation. *Tetrahedron* **61,** 7833–7863 (2005).

15. Allen, A. C., Cooper, D. A., Moore, J. M. & Teer, C. B. Thebaine rearrangements: nonclassical D ring migrations. *J. Org. Chem.* **49,** 3462–3465 (1984).
16. Sipos, A., Berényi, S. & Antus, S. First Synthesis and Utilization of Oripavidine–A Concise and Efficient Route to Important Morphinans and Apomorphines. *Helv. Chim. Acta* **92,** 1359–1365 (2009).
17. Birch, A. J. & Fitton, H. The Preparation and Some Reactions of the Irontricarbonyl Complex of Thebaine. *Aust. J. Chem.* **22,** 971–976 (1969).
18. Bladon, C. M., Ferguson, I. E., Kirby, G. W., Lochead, A. W. & McDougall, D. C. Generation of ethyl thioxoacetate, a dienophilic thioaldehyde. *J. Chem. Soc. Chem. Commun.* 423–425 (1983).
19. Kirby, G. W. & Sclare, A. D. Synthesis of 20-alkyl-8-thiathevinols, opiate agonists derived from 8-thiathevinone, the cycloadduct of thebaine and 2-oxopropanethial. *J Chem Soc Perkin Trans 1* 2329–2338 (1991).
20. Freer, A. A., Kirby, G. W. & Lewis, R. A. Generation of a thioladehyde S-oxide (sulphine) by retro-Diels–Alder reactions. *J. Chem. Soc. Chem. Commun.* 718–719 (1987).
21. Reiner, A. M. & Hegeman, G. D. Metabolism of benzoic acid by bacteria. Accumulation of (-)-3, 5-cyclohexadiene-1, 2-diol-1-carboxylic acid by a mutant strain of Alcaligenes eutrophus. *Biochemistry (Mosc.)* **10,** 2530–2536 (1971).
22. Reineke, W., Otting, W. & Knackmuss, H. J. cis-Dihydrodiols microbially produced from halo- and methylbenzoic acids. *Tetrahedron* **34,** 1708–1714 (1978).

23. Jenkins, G. N., Ribbons, D. W., Widdowson, D. A., Slawin, A. M. & Williams, D. J. Synthetic application of biotransformations: absolute stereochemistry and Diels–Alder reactions of the (1 S, 2 R)-1, 2-dihydroxycyclohexa-3, 5-diene-1-carboxylic acid from Pseudomonas putida. *J. Chem. Soc. [Perkin 1]* 2647–2655 (1995).
24. Lewis, S. E. Applications of biocatalytic arene ipso,ortho cis-dihydroxylation in synthesis. *Chem. Commun.* **50,** 2821 (2014).
25. Charest, M. G., Lerner, C. D., Brubaker, J. D., Siegel, D. R. & Myers, A. G. A Convergent Enantioselective Route to Structurally Diverse 6-Deoxytetracycline Antiobiotics. *Science* **308,** 395–398 (2005).
26. Charest, M. G., Siegel, D. R. & Myers, A. G. Synthesis of (−)-Tetracycline. *J. Am. Chem. Soc.* **127,** 8292–8293 (2005).
27. Ali Khan, M., Mahon, M. F., Stewart, A. J. W. & Lewis, S. E. Iron(0) Tricarbonyl Complexes of Microbially Derived Cyclohexadiene Ligands Containing Quaternary Stereocenters. *Organometallics* **29,** 199–204 (2010).
28. Palframan, M. J., Kociok-Köhn, G. & Lewis, S. E. Total Synthesis of (+)-Grandifloracin by Iron Complexation of a Microbial Arene Oxidation Product. *Org. Lett.* **13,** 3150–3153 (2011).
29. Adams, D. R., Aichinger, C., Collins, J., Rinner, U. & Hudlicky, T. Chemoenzymatic Synthesis of Idesolide from Benzoic Acid. *Synlett* 725–729 (2011).
30. Lee, H. R. *et al.* The Effect of Idesolide on Hippocampus-Dependent Recognition Memory. *Anim. Cells Syst.* **12,** 11–14 (2008).

31. Hwang, J.-H. *et al.* Idesolide inhibits the adipogenic differentiation of mesenchymal cells through the suppression of nitric oxide production. *Eur. J. Pharmacol.* **685,** 218–223 (2012).
32. Hudlicky, T., R. Adams, D., van Kempen, J. & R. Hudlicky, J. Chemoenzymatic Approach to Synthesis of Hydroxylated Pyrrolidines from Benzoic Acid. *HETEROCYCLES* **88,** 1255 (2014).
33. Griffen, J. A. *et al.* New aminocyclitols with quaternary stereocentres via acylnitroso cycloaddition with an ipso,ortho arene dihydrodiol. *Tetrahedron* **69,** 5989–5997 (2013).
34. Pilgrim, S., Kociok-Köhn, G., Lloyd, M. D. & Lewis, S. E. 'Inosaminoacids': novel inositol–amino acid hybrid structures accessed by microbial arene oxidation. *Chem. Commun.* **47,** 4799 (2011).
35. Palframan, M. J., Kociok-Köhn, G. & Lewis, S. E. Photooxygenation of a Microbial Arene Oxidation Product and Regioselective Kornblum-DeLaMare Rearrangement: Total Synthesis of Zeylenols and Zeylenones. *Chem. - Eur. J.* **18,** 4766–4774 (2012).
36. Kaou, A. M. *et al.* Antimalarial compounds from the aerial parts of *Flacourtia indica* (Flacourtiaceae). *J. Ethnopharmacol.* **130,** 272–274 (2010).
37. Sashidhara, K. V. *et al.* Isolation and identification of β-hematin inhibitors from *Flacourtia indica* as promising antiplasmodial agents. *Eur. J. Med. Chem.* **60,** 497–502 (2013).

38. Gibbons, S. *et al.* Benzoylated derivatives of 2-β-glucopyranosyloxy-2, 5-dihydroxybenzyl alcohol from Xylosma flexuosum: structure and relative configuration of xylosmin. *J. Nat. Prod.* **58,** 554–559 (1995).
39. Bourjot, M. *et al.* Flacourtosides A–F, Phenolic Glycosides Isolated from *Flacourtia ramontchi*. *J. Nat. Prod.* **75,** 752–758 (2012).
40. Birch, A. J., Kelly, L. F. & Liepa, A. J. Lateral Control of Skeletal Rearrangement by Complexation of Thebaine with Fe(CO)3. *Tetrahedron Lett.* **26,** 501–504 (1985).
41. Doyaguez, E. Boron Tribromide. *Synlett* **10,** 1636–1637 (2005).
42. Vickery, E. H., Pahler, L. F. & Eisenbraun, E. J. Selective O-demethylation of catechol ethers. Comparison of boron tribromide and iodotrimethylsilane. *J. Org. Chem.* **44,** 4444–4446 (1979).
43. Hartmann, R. Biaryl Derivatives as Selective 17Beta-Hydroxysteroid Dehydrogenase Type 2 Inhibitors.
44. Andre, J. D., Dormoy, J. R. & Heymes, A. O-Demethylation of opioid derivatives with methane sulfonic-acid methionine - application to the synthesis of naloxone and analogs. *Synth. Commun.* **22,** 2313–2327 (1992).
45. Hilli, F., White, J. M. & Rizzacasa, M. A. Formal total synthesis of the myxobacteria metabolite apicularen A via a transannular oxy-Michael addition. *Tetrahedron* **67,** 5054–5068 (2011).
46. Sudo, Y., Arai, S. & Nishida, A. Facile and Regioselective Dealkylation of Alkyl Aryl Ethers Using Niobium(V) Pentachloride. *Eur. J. Org. Chem.* **2006,** 752–758 (2006).

47. Marchetti, F., Pampaloni, G. & Zacchini, S. Fragmentation of oxygen-containing molecules via C–O bond cleavage promoted by coordination to niobium and tantalum pentahalides. *Dalton Trans.* 6759 (2009). doi:10.1039/b905023j

48. Olah, G. A., Narang, S. C., Gupta, B. B. & Malhotra, R. Synthetic methods and reactions. 62. Transformations with chlorotrimethylsilane/sodium iodide, a convenient in situ iodotrimethylsilane reagent. *J. Org. Chem.* **44,** 1247–1251 (1979).

49. Yadav, J. S., Reddy, B. S., Madan, C. & Hashim, S. R. A Mild and Chemoselective Dealkylation of Alkyl Aryl Ethers by Cerium (III) Chloride-NaI. *Chem. Lett.* 738–739 (2000).

50. Shvo, Y. & Hazum, E. A simple method for the disengagement of organic ligands from iron complexes. *J Chem Soc Chem Commun* 336–337 (1974).

51. Knolker, H.-J., Goesmann, H. & Klauss, R. A Novel Method for the Demethylation of Tricarbonyliron-Diene Complexes by a Photolytically Induced Ligand Exchange Reaction with Acetonitrile. *Angew. Chem. Int. Ed.* **38,** 702–705 (1999).

52. Murphy, B. *et al.* Conversion of Thebaine to Oripavine and Other Useful Intermediates for the Semisynthesis of Opiate-Derived Agents: Synthesis of Hydromorphone. *Adv. Synth. Catal.* **356,** 2679–2687 (2014).

53. Myers, A. G., Siegel, D. R., Buzard, D. J. & Charest, M. G. Synthesis of a Broad Array of Highly Functionalized, Enantiomerically Pure Cyclohexanecarboxylic Acid Derivatives by Microbial Dihydroxylation of Benzoic Acid and Subsequent Oxidative and Rearrangement Reactions. *Org. Lett.* **3,** 2923–2926 (2001).

54. Banwell, M. G., Edwards, A. J., Lupton, D. W. & Whited, G. Whole-Cell Biotransformation of *m* -Ethyltoluene into 1 *S* ,6 *R* -5-Ethyl-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylic Acid as an Approach to the C-Ring of the Binary Indole–Indoline Alkaloid Vinblastine. *Aust. J. Chem.* **58,** 14 (2005).

55. Adams, D. R. The Use of Ipso-dihydrodiols Enzymatcally Derived from Benzoic Acid in Enantioselective Synthesis. Approaches to Total Synthesis of Vinca Alkaloids. (Brock, 2014).

56. Ross, A. M. *et al.* Vinyl Epoxide Hydrolysis Reactions. *J. Am. Chem. Soc.* **104,** 1658–1665 (1982).

57. Lundin, A., Panas, I. & Ahlberg, E. A Mechanistic Investigation of Ethylene Oxide Hydrolysis to Ethanediol. *J. Phys. Chem. A* **111,** 9087–9092 (2007).

58. Mel'nik, L. V. *et al.* Synthesis of diols from 1,2-epoxy-3-butene. *Pet. Chem.* **47,** 201–204 (2007).

59. Venkat Narsaiah, A., Reddy, B. V. S., Premalatha, K., Reddy, S. S. & Yadav, J. S. Bismuth(III)-Catalyzed Hydrolysis of Epoxides and Aziridines: an Efficient Synthesis of vic-diols and β-Amino Alcohols. *Catal. Lett.* **131,** 480–484 (2009).

60. Moorthy, J. N., Singhal, N. & Senapati, K. Oxidative cleavage of vicinal diols: IBX can do what Dess?Martin periodinane (DMP) can. *Org. Biomol. Chem.* **5,** 767 (2007).

61. McKittrick, B. A. & Ganem, B. Advances in the Chemistry of 2,3-Epoxy Alcohols. New Methodology for Contra-Trans-Diaxial Opening and Selective Enediol Oxidation. *J. Org. Chem.* **50,** 5897–5898 (1985).

62. Hamada, S., Furuta, T., Wada, Y. & Kawabata, T. Chemoselective Oxidation by Electronically Tuned Nitroxyl Radical Catalysts. *Angew. Chem. Int. Ed.* **52,** 8093–8097 (2013).

63. William, J. M., Kuriyama, M. & Onomura, O. Boronic Acid-Catalyzed Selective Oxidation of 1,2-Diols to α-Hydroxy Ketones in Water. *Adv. Synth. Catal.* **356,** 934–940 (2014).

64. Liu, Z., Chen, Z.-C. & Zheng, Q.-G. Mild Oxidation of Alcohols with *O* -Iodoxybenzoic Acid (IBX) in Ionic Liquid 1-Butyl-3-methyl-imidazolium Chloride and Water. *Org. Lett.* **5,** 3321–3323 (2003).

65. Donohoe, T. J. *et al.* Directed Dihydroxylation of Cyclic Allylic Alcohols and Trichloroacetamides Using $OsO_4$ /TMEDA. *J. Org. Chem.* **67,** 7946–7956 (2002).

66. Csatayová, K. *et al.* Highly Diastereoselective and Stereodivergent Dihydroxylations of Acyclic Allylic Amines: Application to the Asymmetric Synthesis of 3,6-Dideoxy-3-amino- L -talose. *Org. Lett.* **13,** 2606–2609 (2011).

67. Walsh, K., Sneddon, H. F. & Moody, C. J. Solar Photochemical Oxidations of Benzylic and Allylic Alcohols Using Catalytic Organo-oxidation with DDQ: Application to Lignin Models. *Org. Lett.* **16,** 5224–5227 (2014).

68. Shafiee, A., Lalezari, I., Assadi, F. & Khalafi, F. Alkaloids of Papaver orientale L. *J. Pharm. Sci.* **66,** 1050–1052 (1977).

69. Fischer, T. C. M., Leisch, H. G. & Mihovilovic, M. D. Intramolecular Diels–Alder cyclization of biodihydroxylated benzoic acid derivatives towards novel heterocyclic scaffolds. *Monatshefte Für Chem. - Chem. Mon.* **141,** 699–707 (2010).

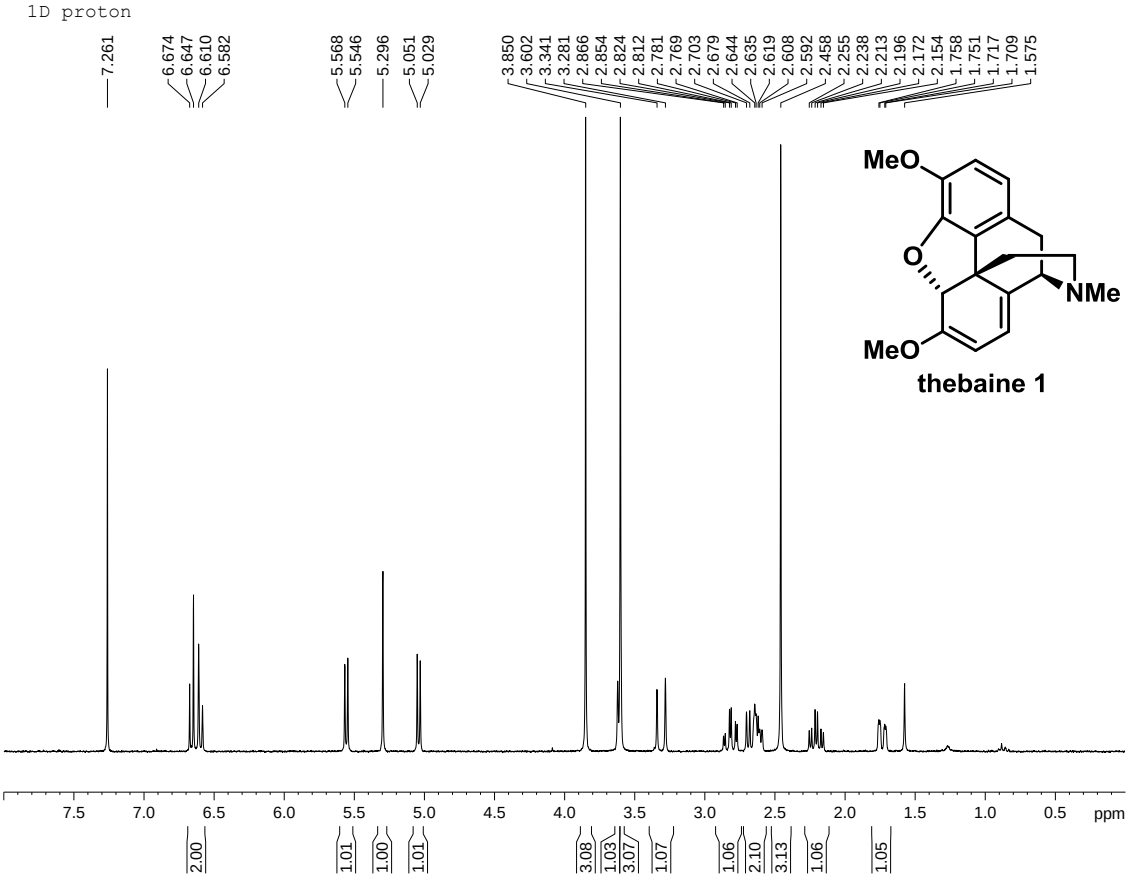
70. Répichet, S., Zwick, A., Vendier, L., Le Roux, C. & Dubac, J. A practical, cheap and environmentally friendly preparation of bismuth (III) trifluoromethanesulfonate. *Tetrahedron Lett.* **43,** 993–995 (2002).

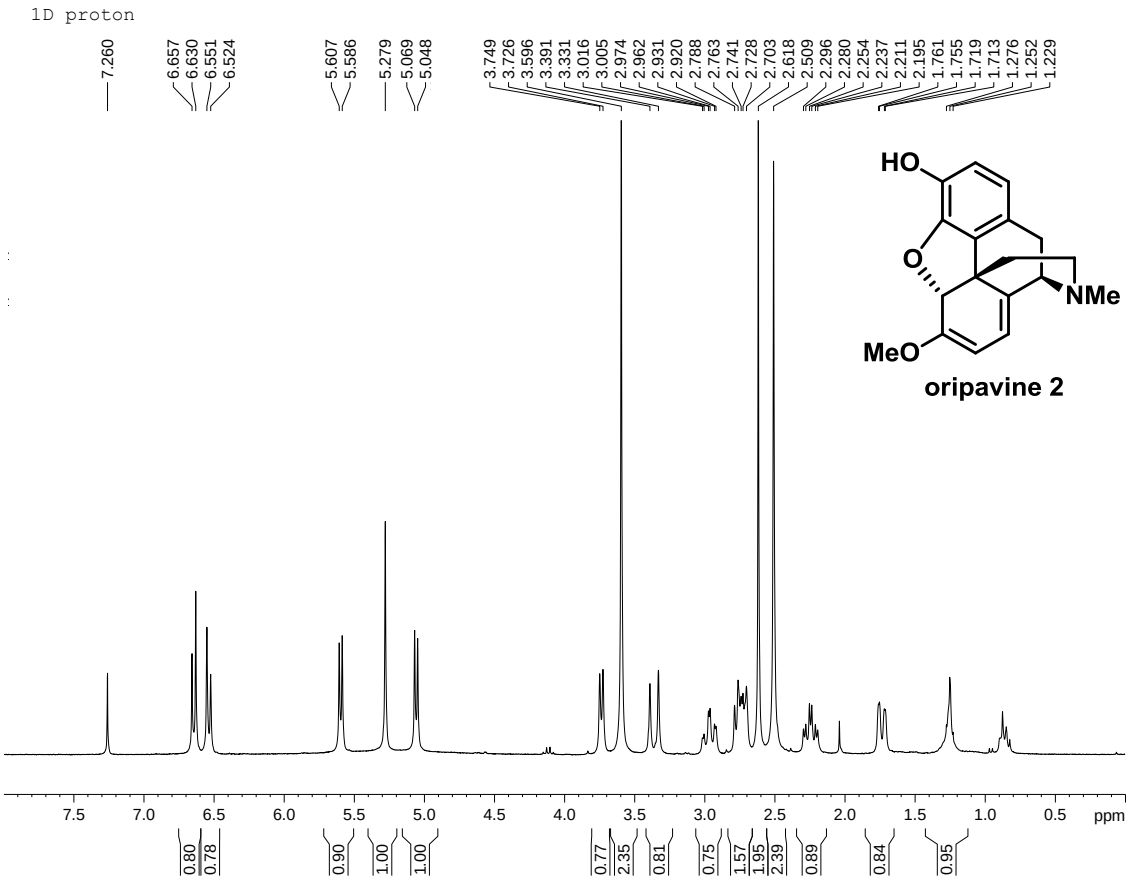
71. THE DESS-MARTIN PERIODINANE: 1,1,1-TRIACETOXY-1,1-DIHYDRO-1,2-BENZIODOXOL-3(1H)-ONE. *Org. Synth.* **77,** 141 (2000).

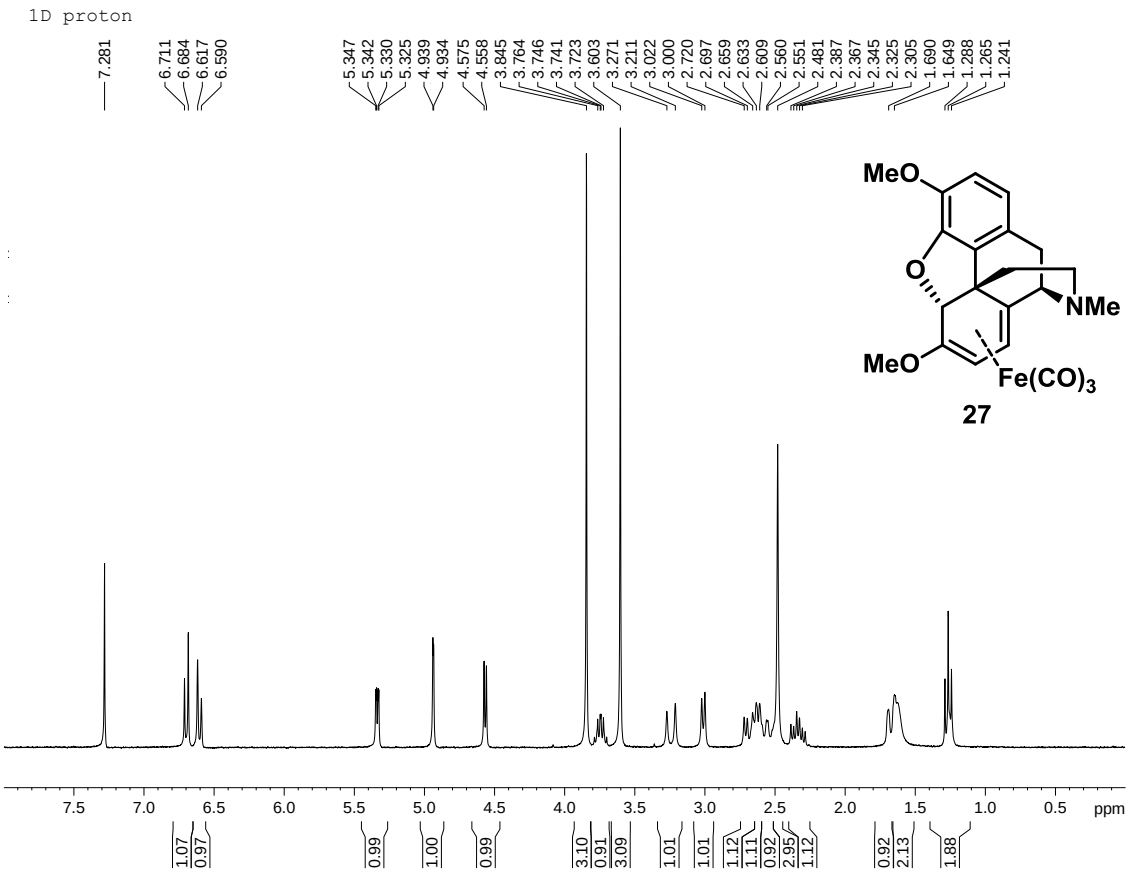
72. Baba, K. *et al.* Kinetic Study of ThermalZ toE Isomerization Reactions of Azobenzene and 4-Dimethylamino-4'-nitroazobenzene in Ionic Liquids [1-R-3-Methylimidazolium Bis(trifluoromethylsulfonyl)imide with R=Butyl, Pentyl, and Hexyl]. *Chem. - Eur. J.* **12,** 5328–5333 (2006).

73. NITROSOMETHYLUREA. *Org. Synth.* **15,** 48 (1935).

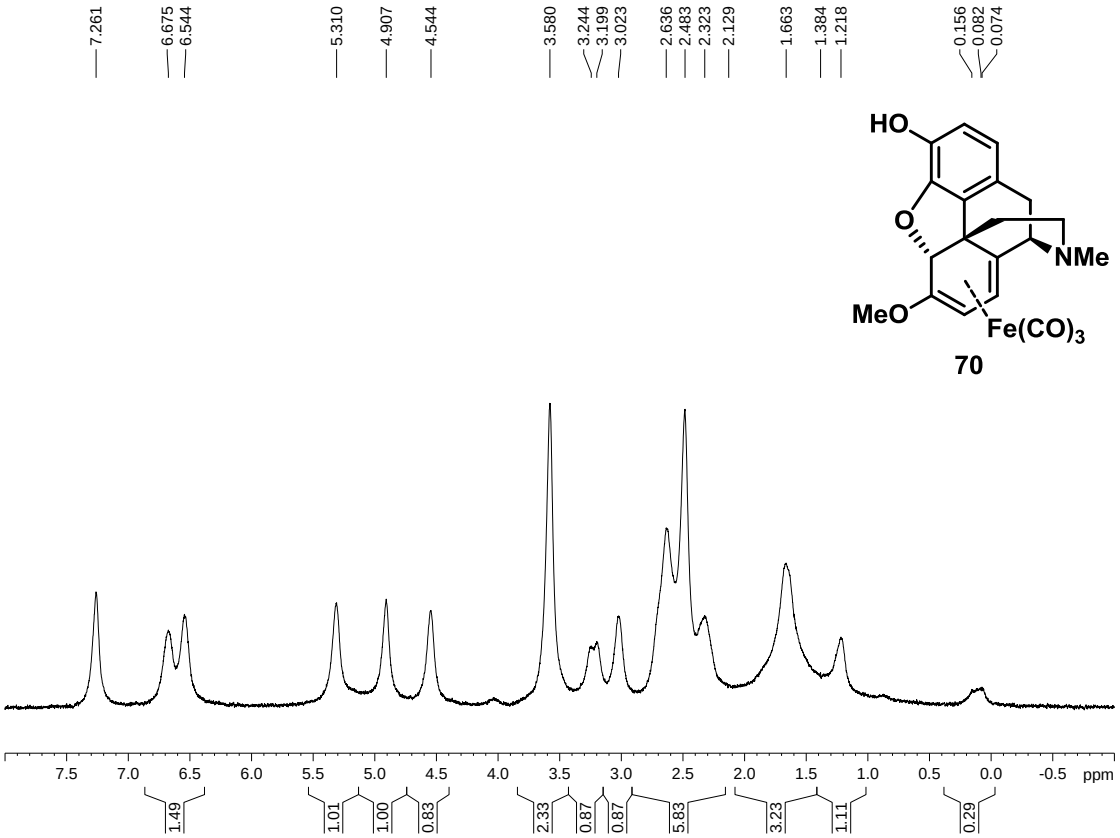
74. DIAZOMETHANE. *Org. Synth.* **15,** 3 (1935).


1D proton
7.261
6.674
6.647
6.610
6.582
5.568
5.546
5.296
5.051
5.029
3.850
3.602
3.341
3.281
2.866
2.854
2.824
2.812
2.781
2.769
2.703
2.679
2.644
2.635
2.619
2.608
2.592
2.458
2.255
2.238
2.213
2.196
2.172
2.154
1.758
1.751
1.717
1.709
1.575
MeO
O
NMe
MeO
thebaine 1
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00
1.01
1.00
1.01
3.08
1.03
3.07
1.07
1.06
2.10
3.13
1.06
1.05


1D proton
7.260
6.657
6.630
6.551
6.524
5.607
5.586
5.279
5.069
5.048
3.749
3.726
3.596
3.391
3.331
3.016
3.005
2.974
2.962
2.931
2.920
2.788
2.763
2.741
2.728
2.703
2.618
2.509
2.296
2.280
2.254
2.237
2.211
2.195
1.761
1.755
1.719
1.713
1.276
1.252
1.229
HO
O
NMe
MeO
oripavine 2
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.80
0.78
0.90
1.00
1.00
0.77
2.35
0.81
0.75
1.57
1.95
2.39
0.89
0.84
0.95

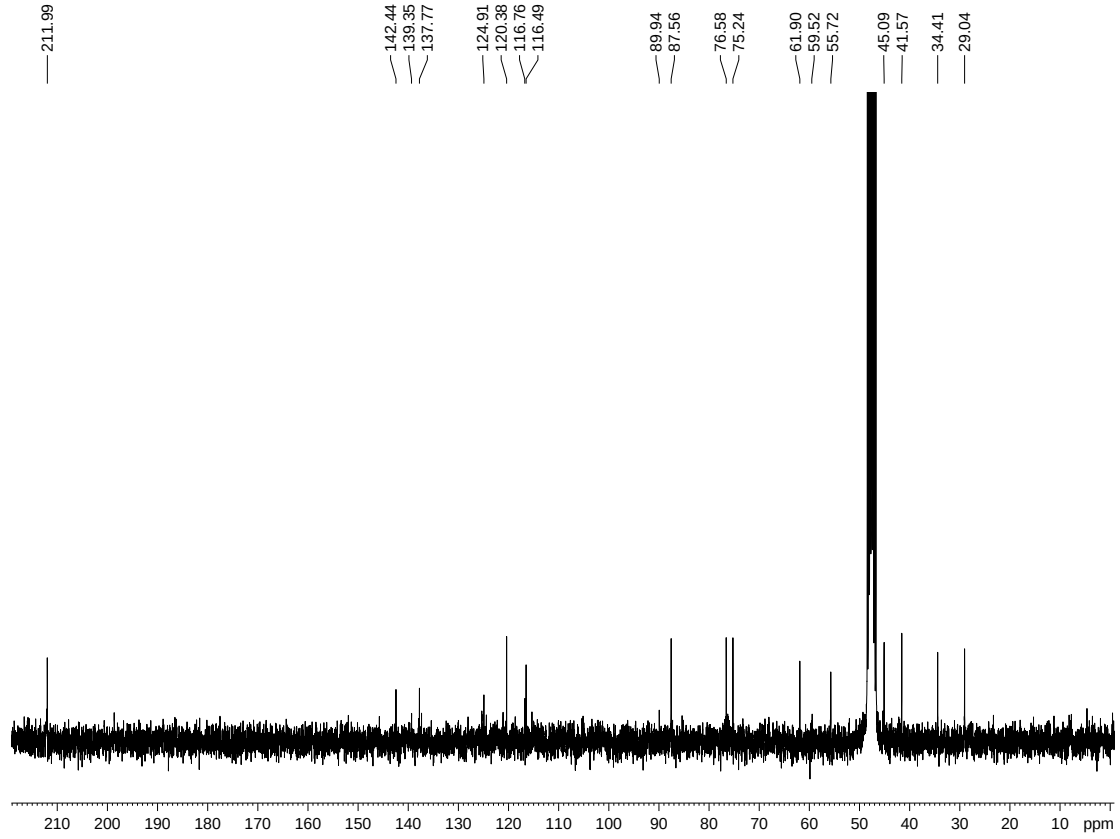

1D proton
7.281
6.711
6.684
6.617
6.590
5.347
5.342
5.330
5.325
4.939
4.934
4.575
4.558
3.845
3.764
3.746
3.741
3.723
3.603
3.271
3.211
3.022
3.000
2.720
2.697
2.659
2.633
2.609
2.560
2.551
2.481
2.387
2.367
2.345
2.325
2.305
1.690
1.649
1.288
1.265
1.241
MeO
O
NMe
MeO
Fe(CO)3
27
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.07
0.97
0.99
1.00
0.99
3.10
0.91
3.09
1.01
1.01
1.12
1.11
0.92
2.95
1.12
0.92
2.13
1.88

1D proton

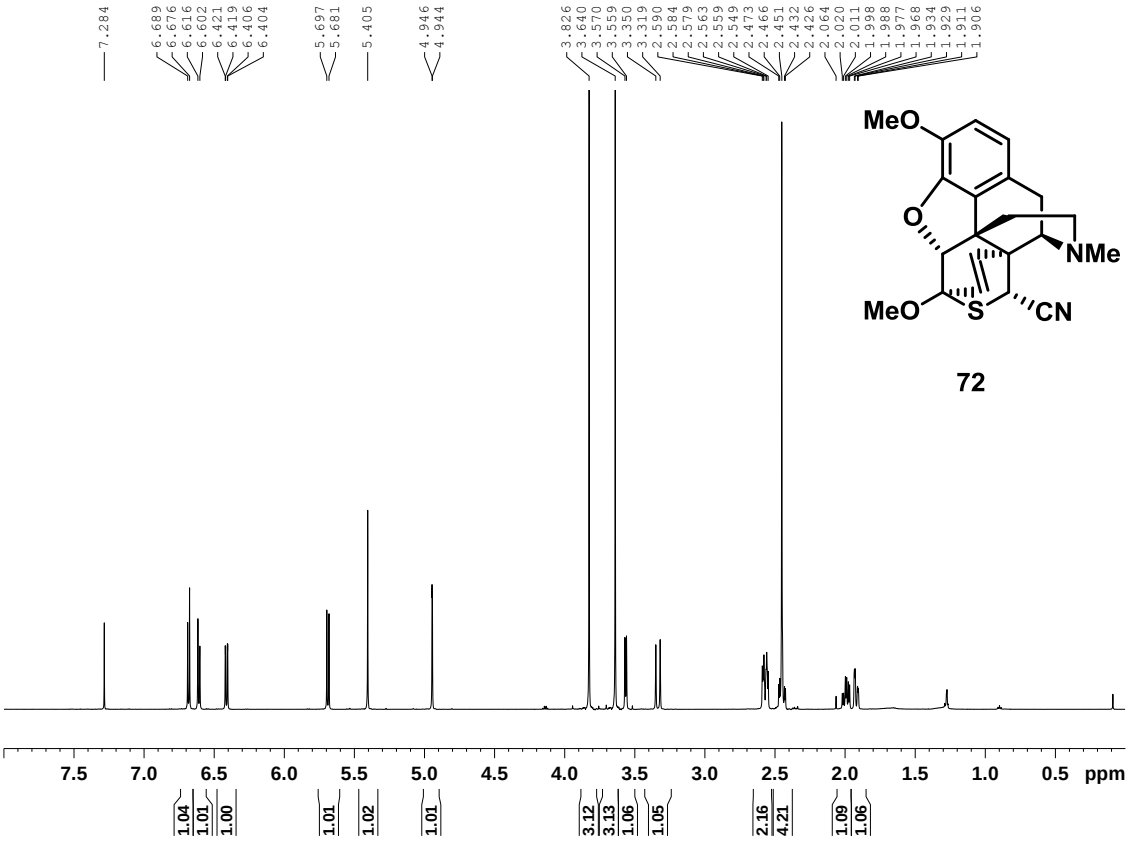



**70**

1D carbon with proton decoupling

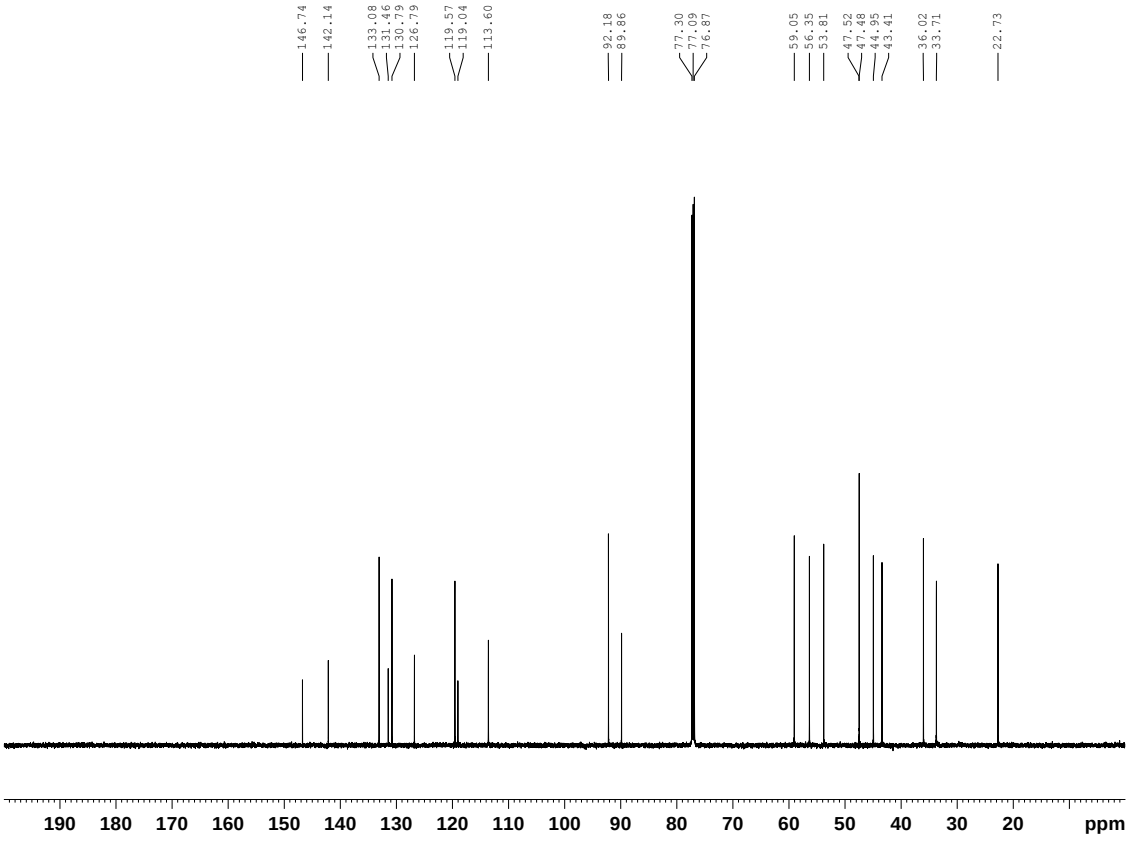


1d proton

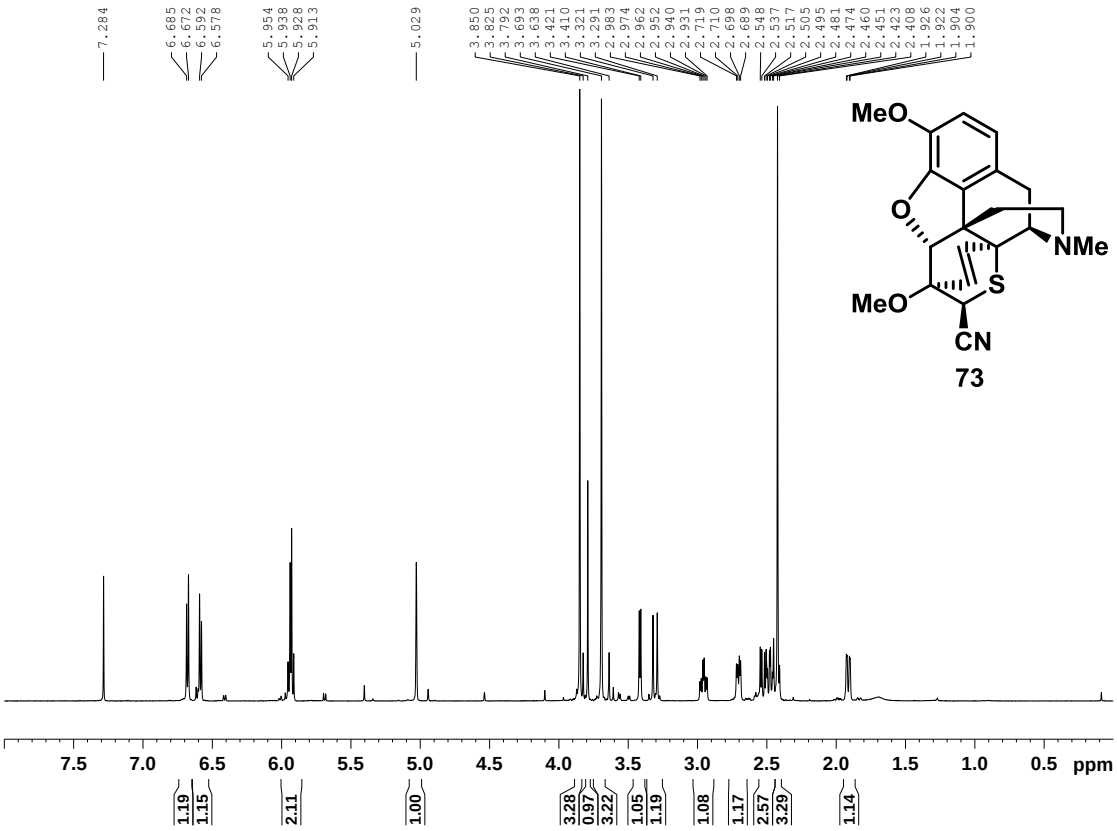



72

1d carbon with proton decoupling

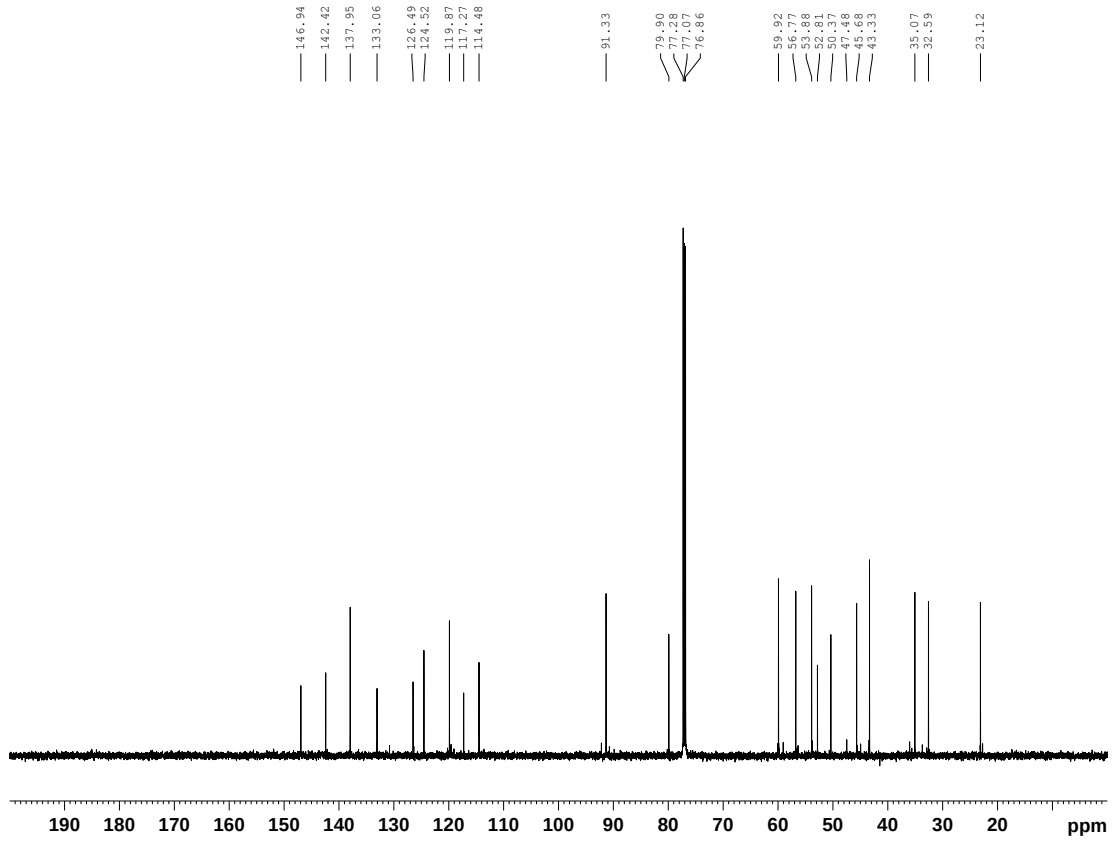


1d proton

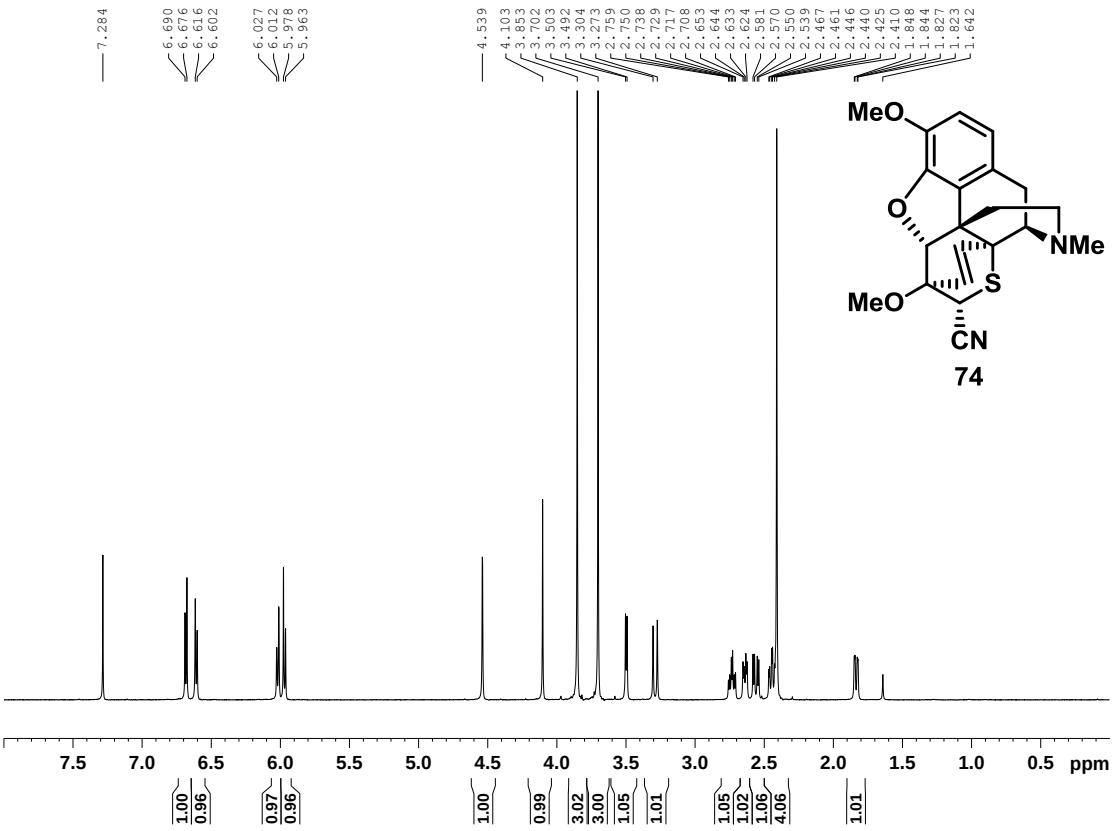



73

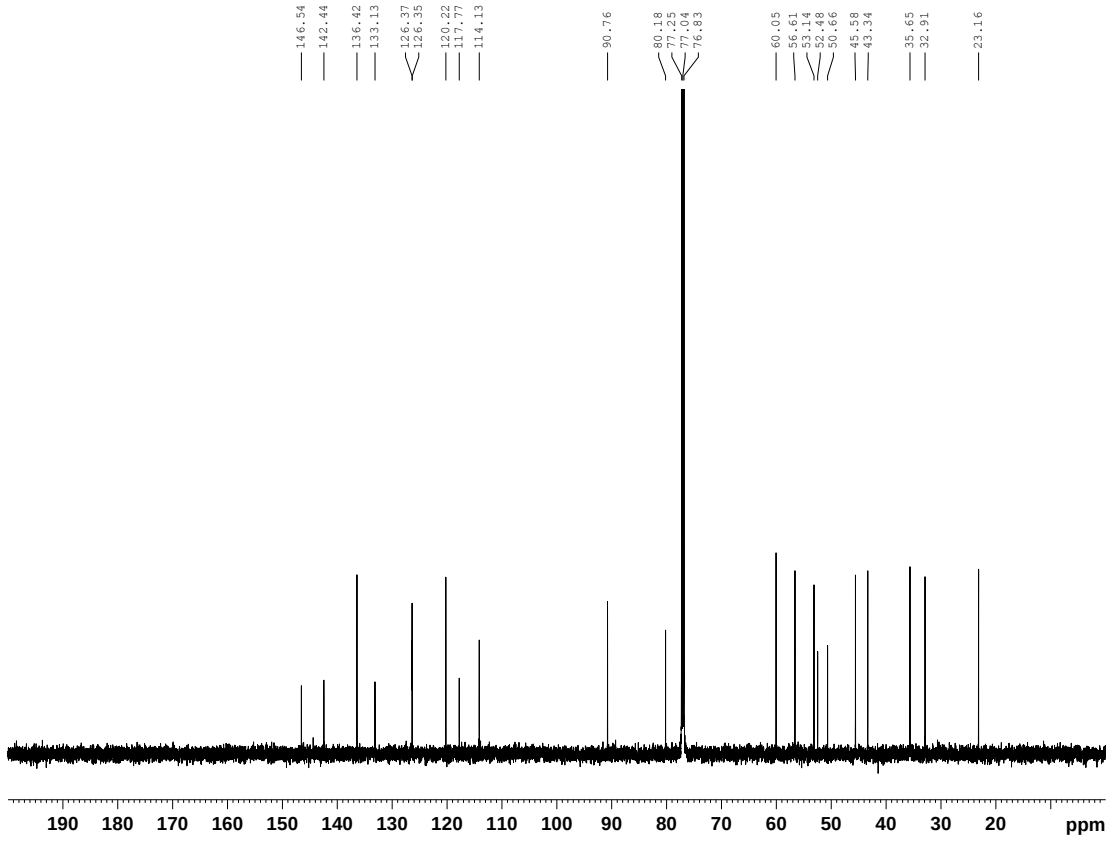
1d carbon with proton decoupling



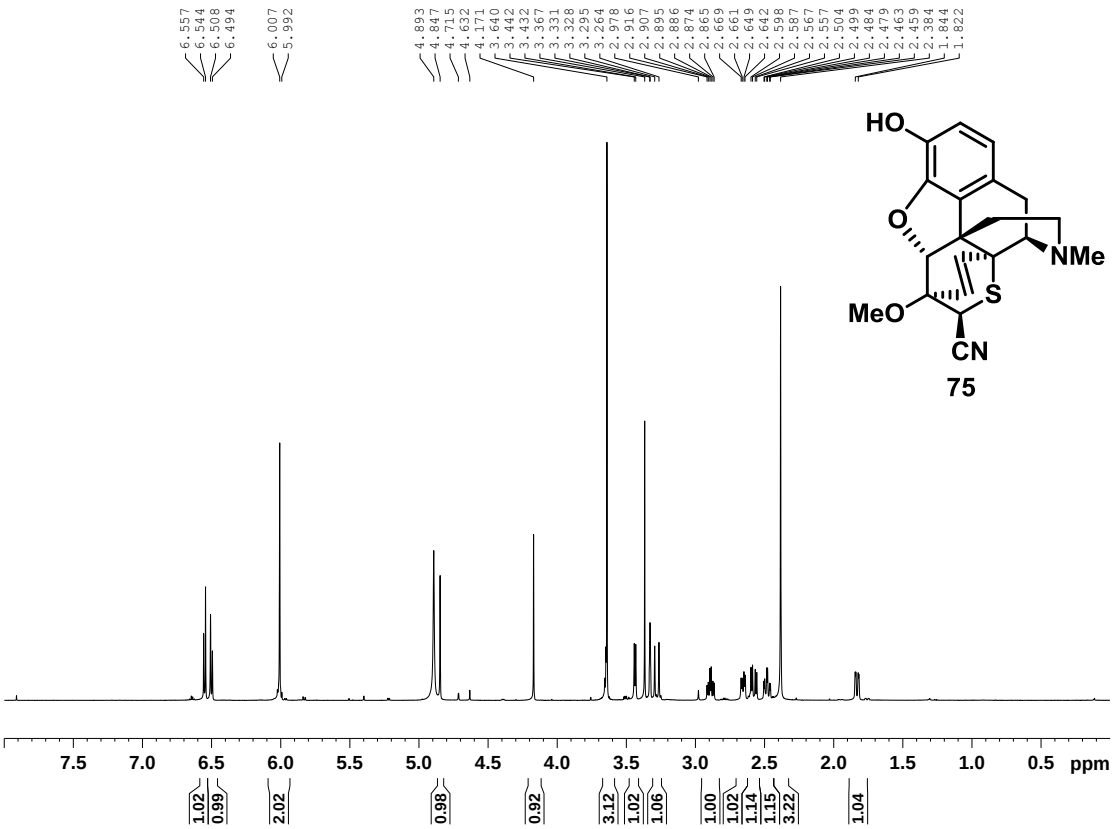
1d proton



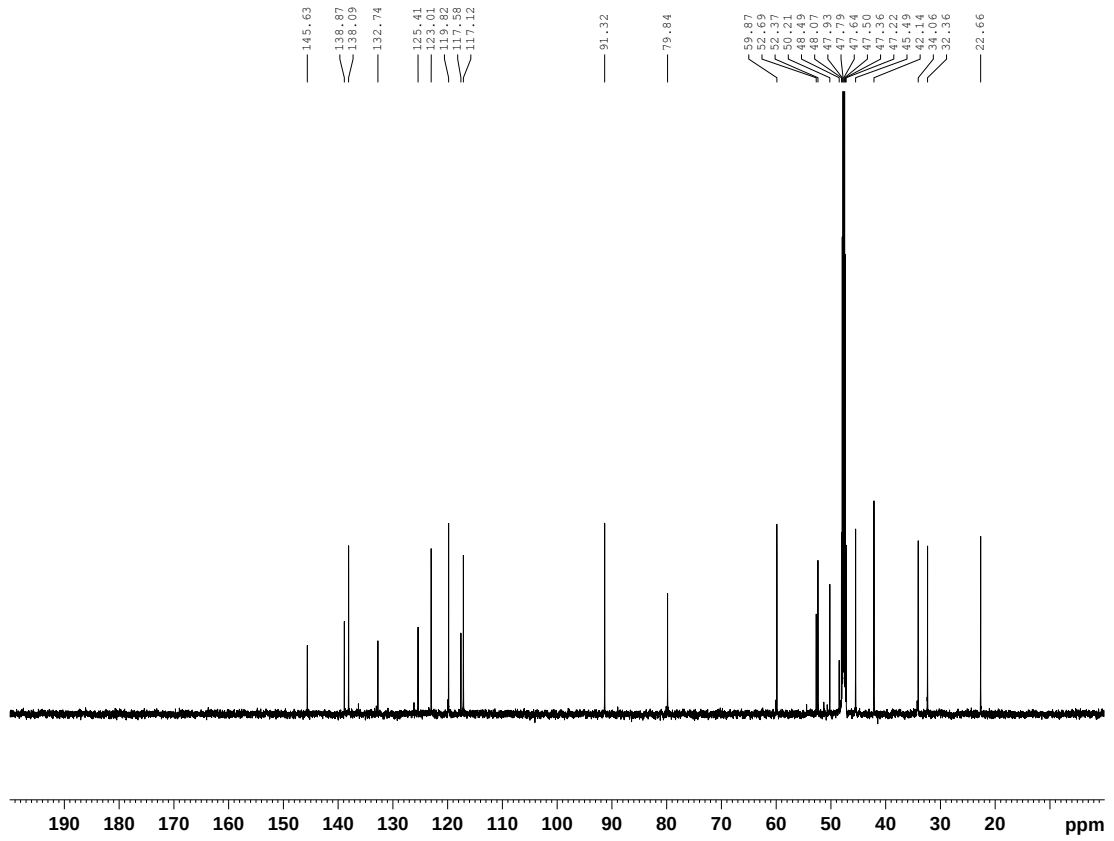

1d carbon with proton decoupling



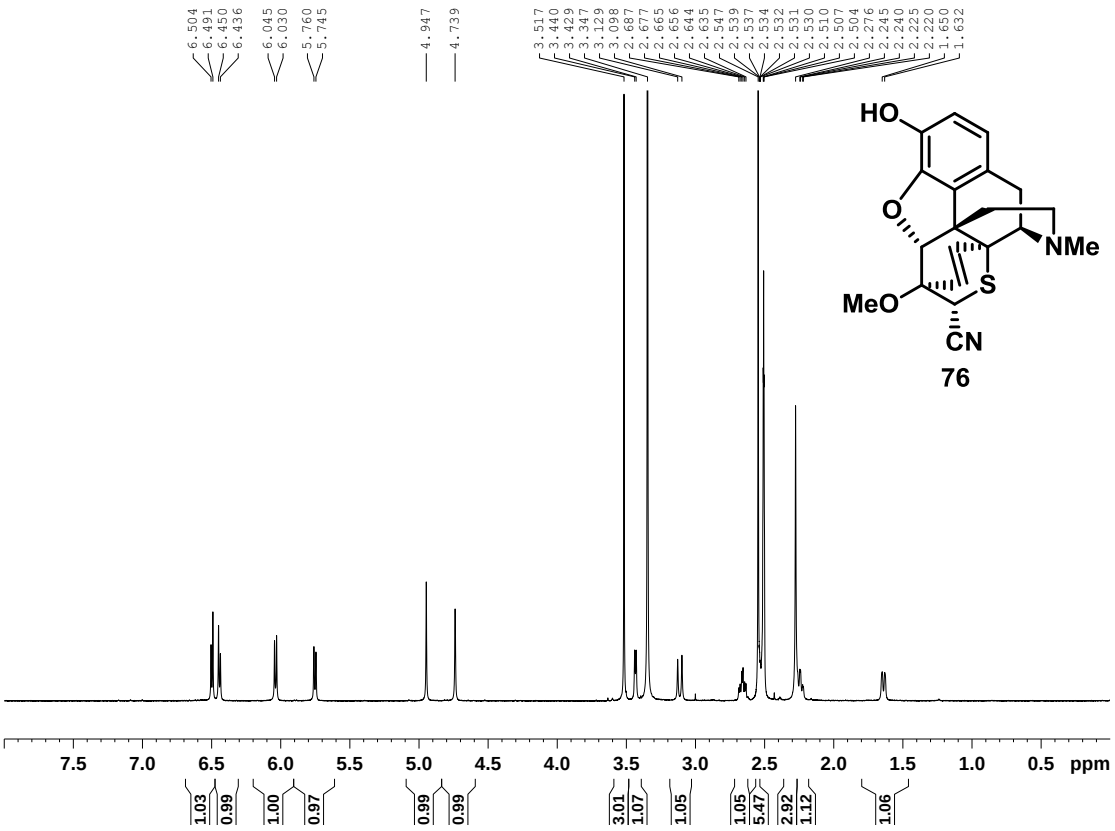
1d proton



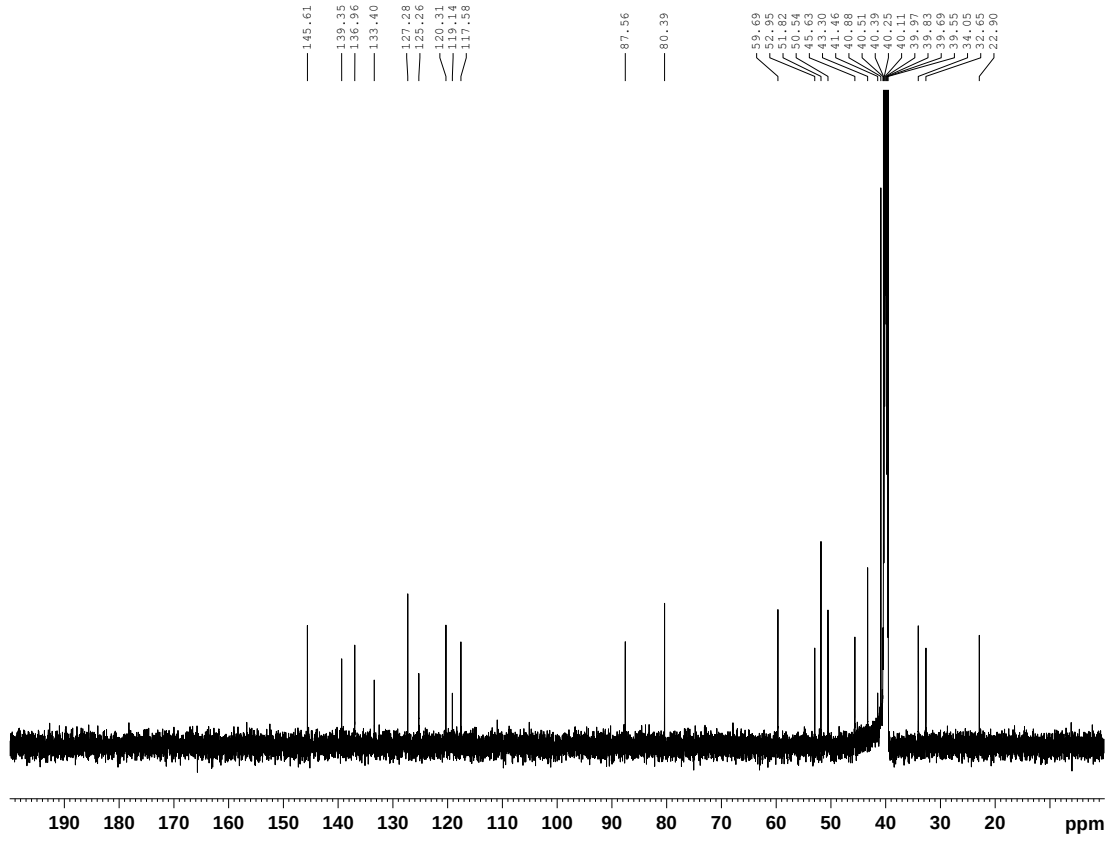

1d carbon with proton decoupling



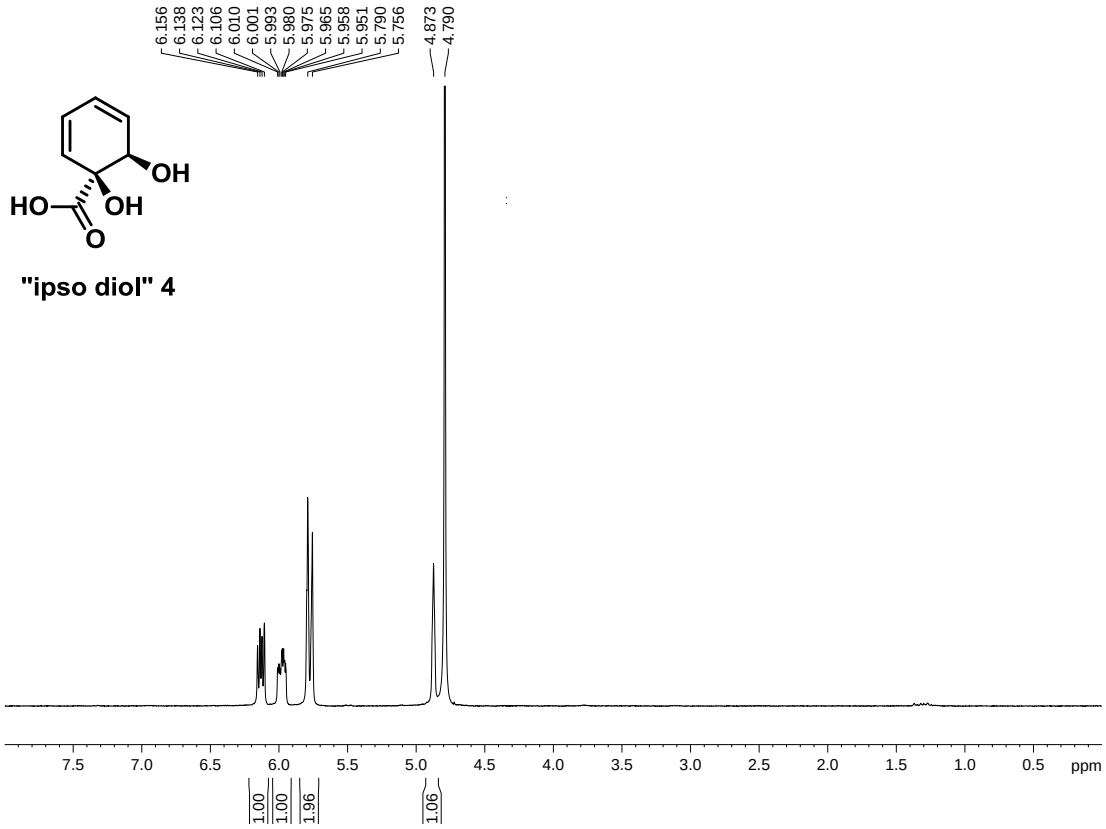
1d proton



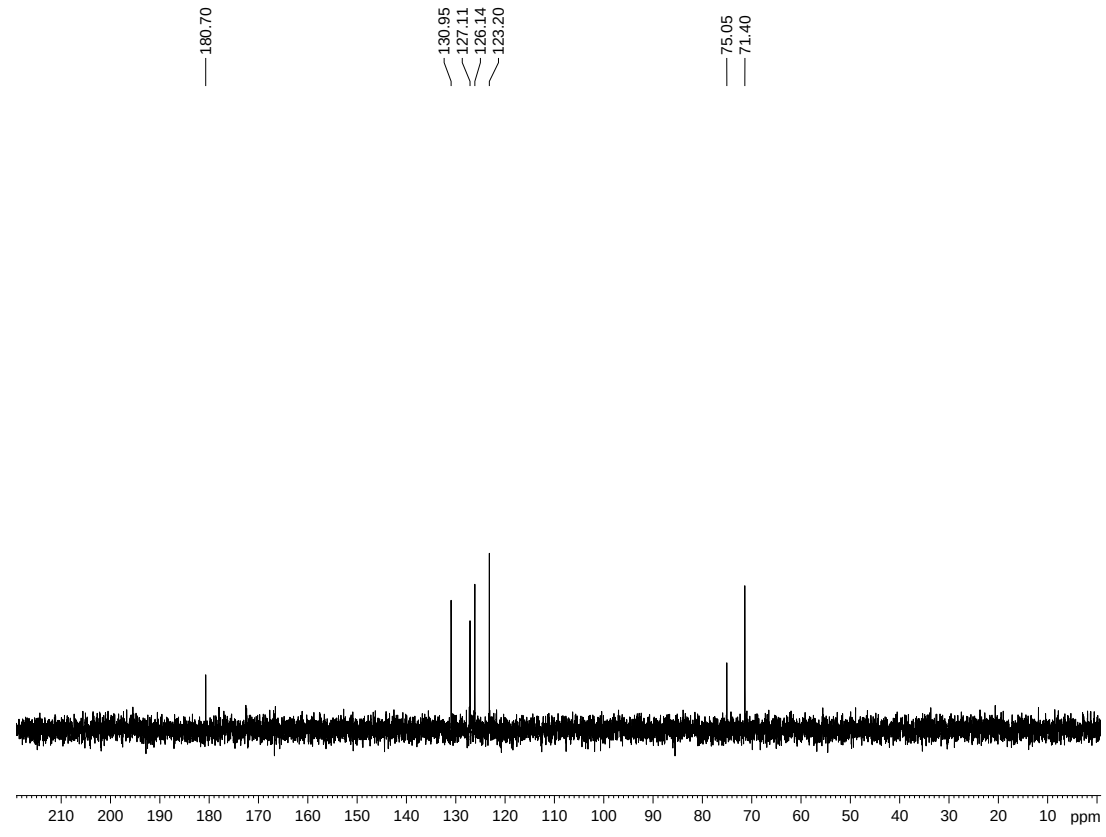

1d carbon with proton decoupling

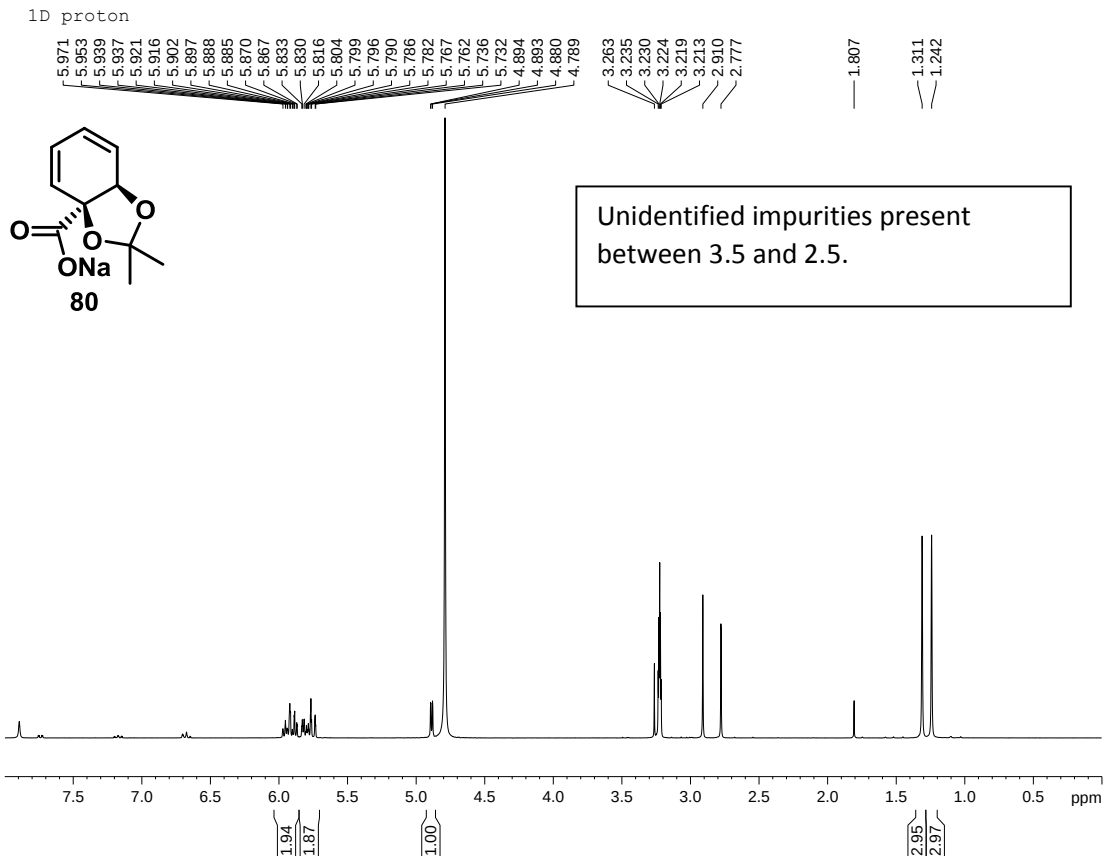


1D proton



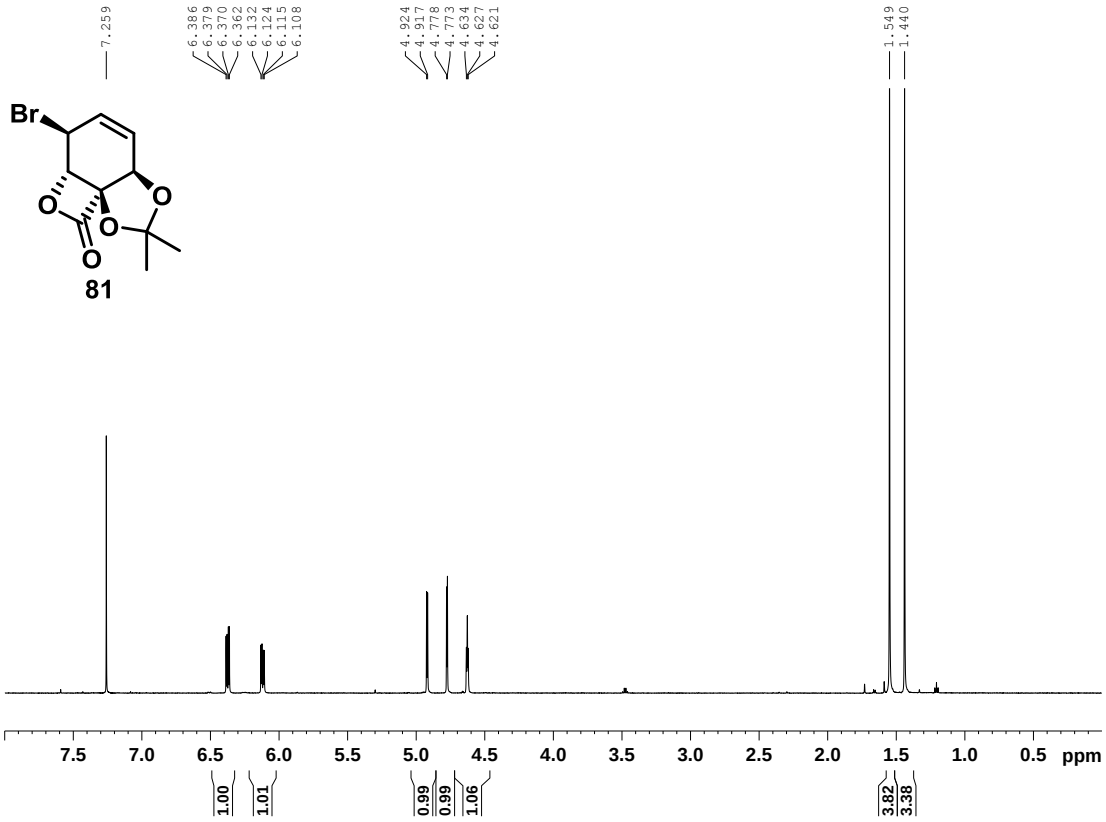

1D carbon with proton decoupling



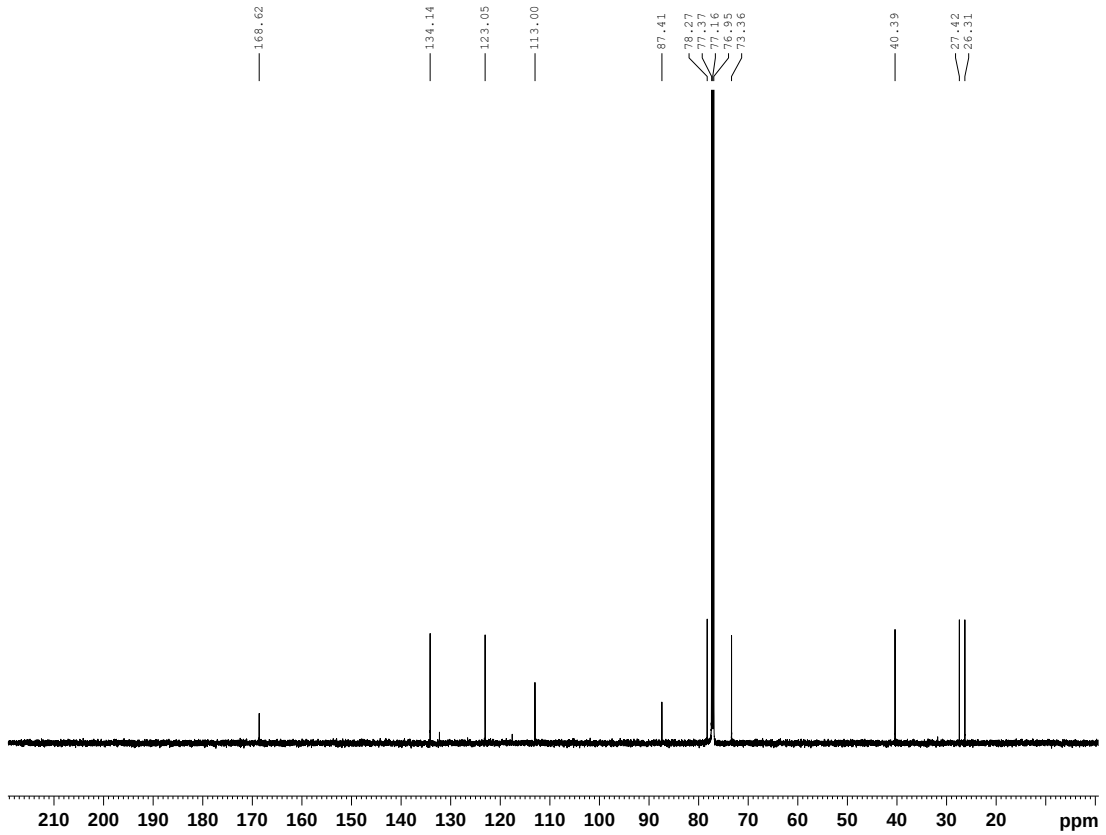

1D proton
5.971
5.953
5.939
5.937
5.921
5.916
5.902
5.897
5.888
5.885
5.870
5.867
5.833
5.830
5.816
5.804
5.799
5.796
5.790
5.786
5.782
5.767
5.762
5.736
5.732
4.894
4.893
4.880
4.789
3.263
3.235
3.230
3.224
3.219
3.213
2.910
2.777
1.807
1.311
1.242
O
O
O
ONa
80
Unidentified impurities present between 3.5 and 2.5.
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.94
1.87
1.00
2.95
2.97

X

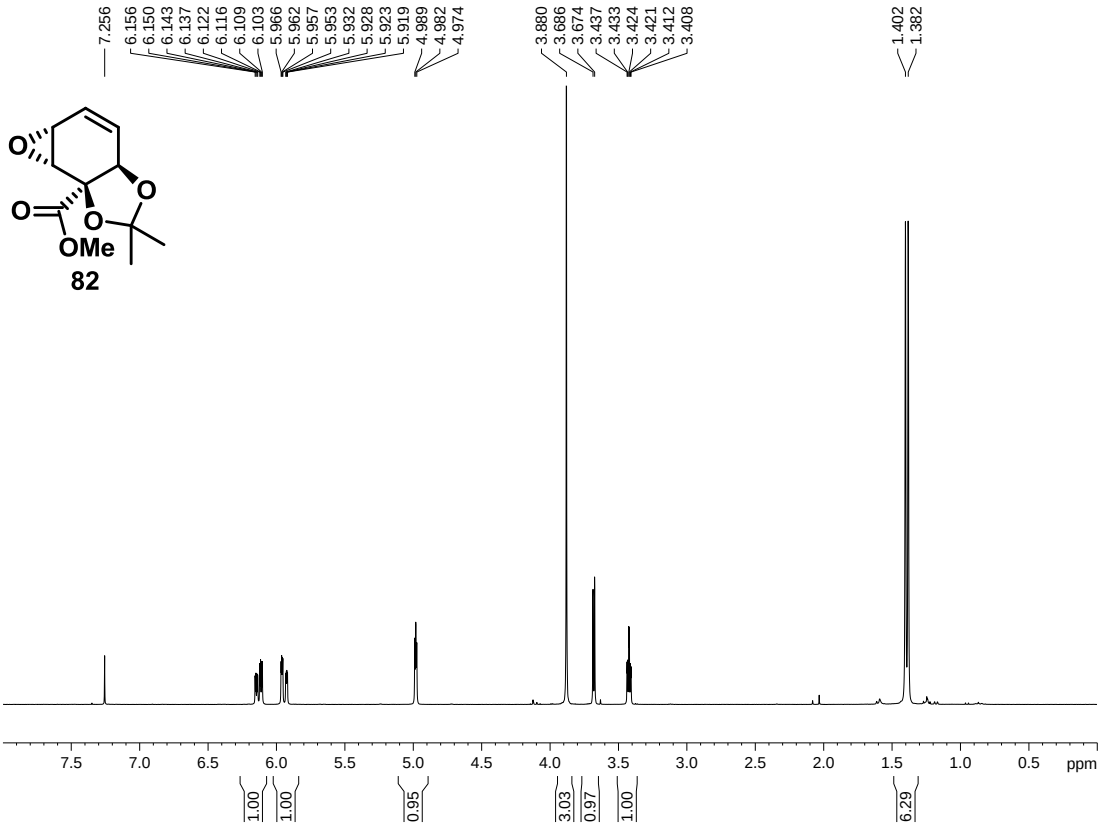
1d proton



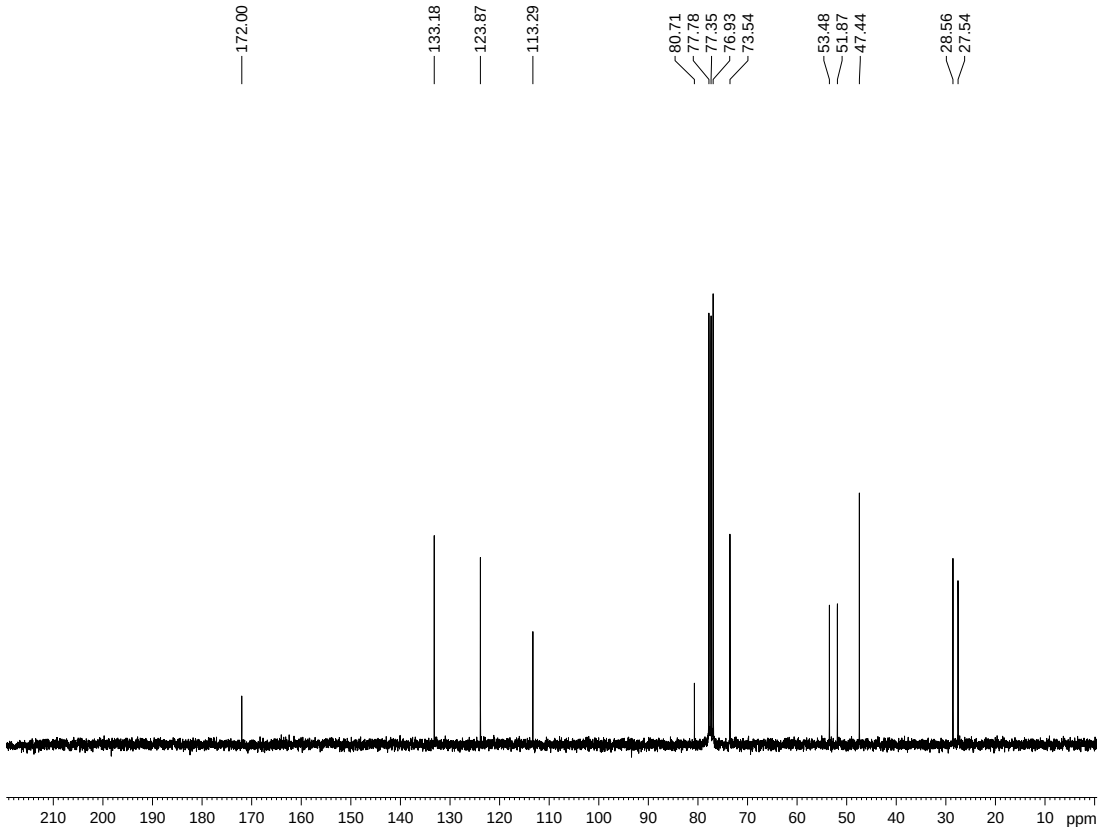

1d carbon with proton decoupling



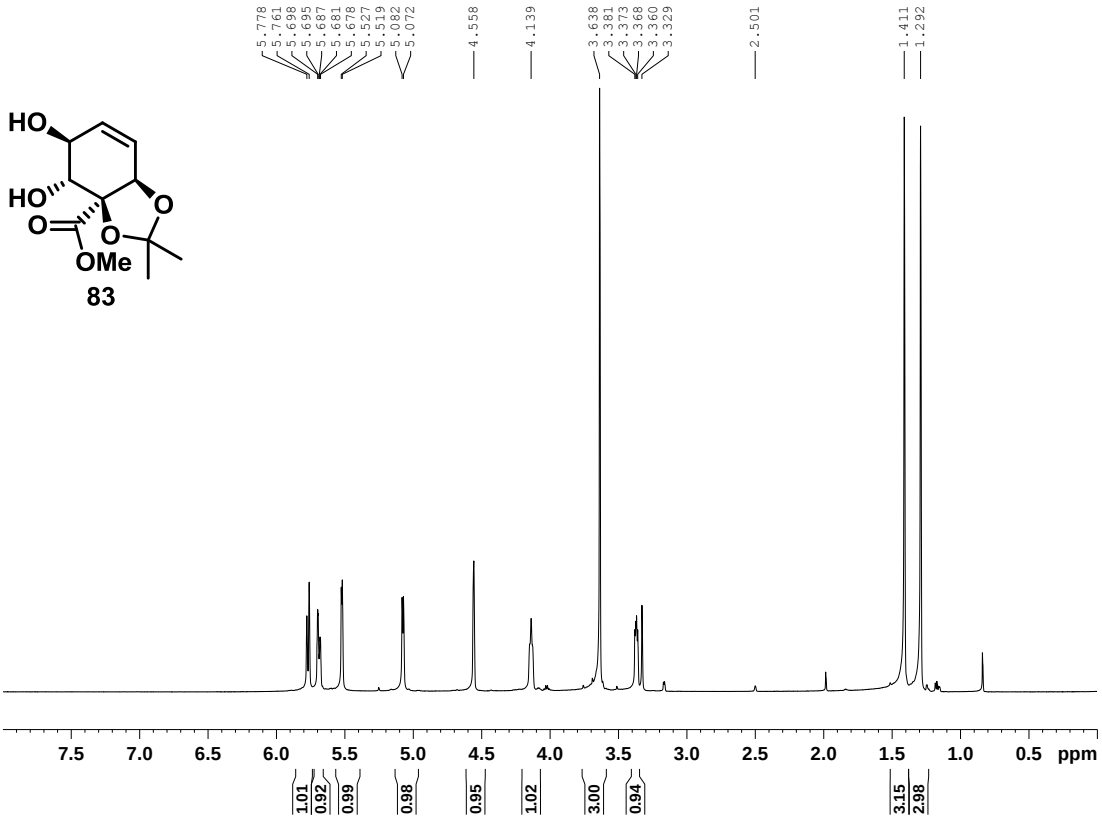
1D proton




1D carbon with proton decoupling

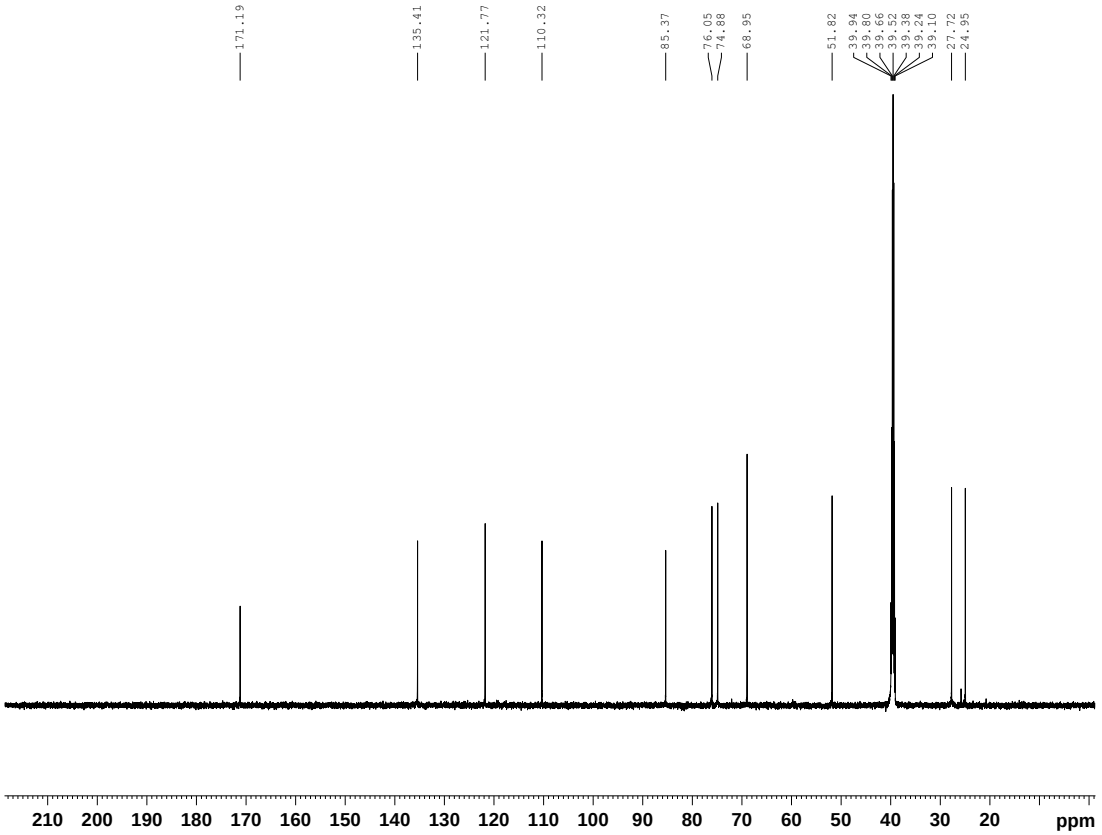


1d proton

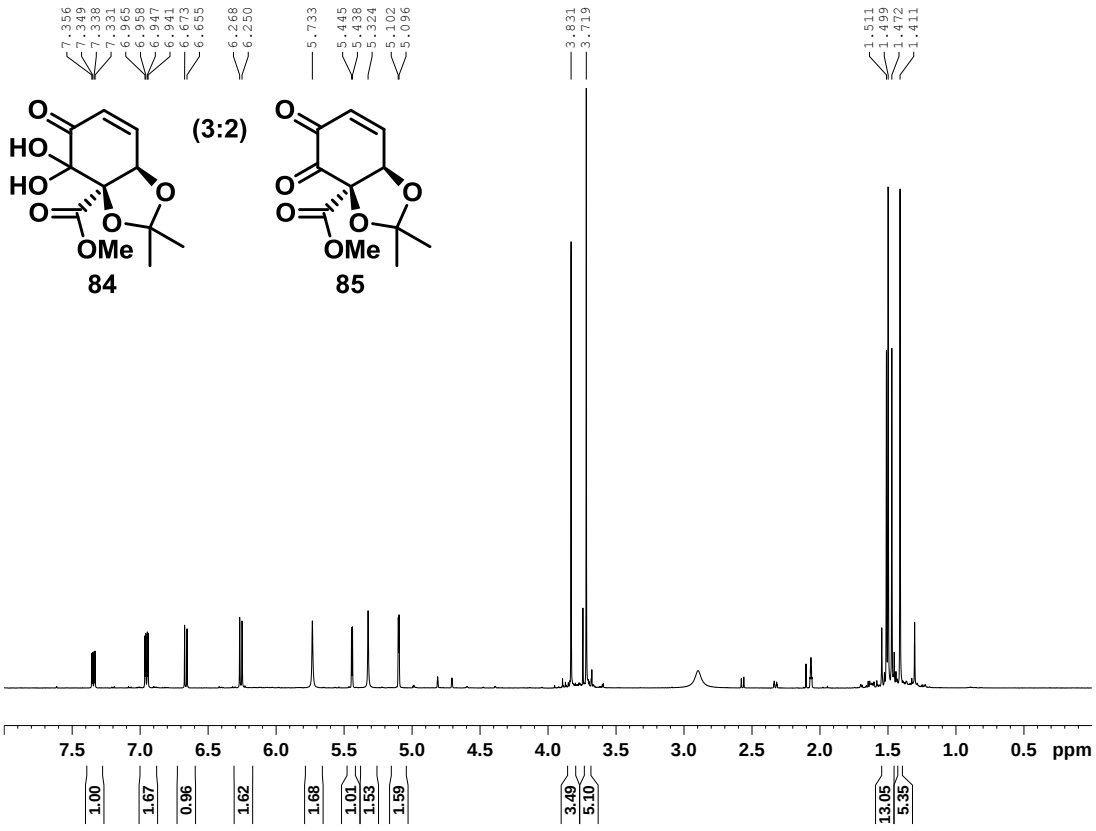



83

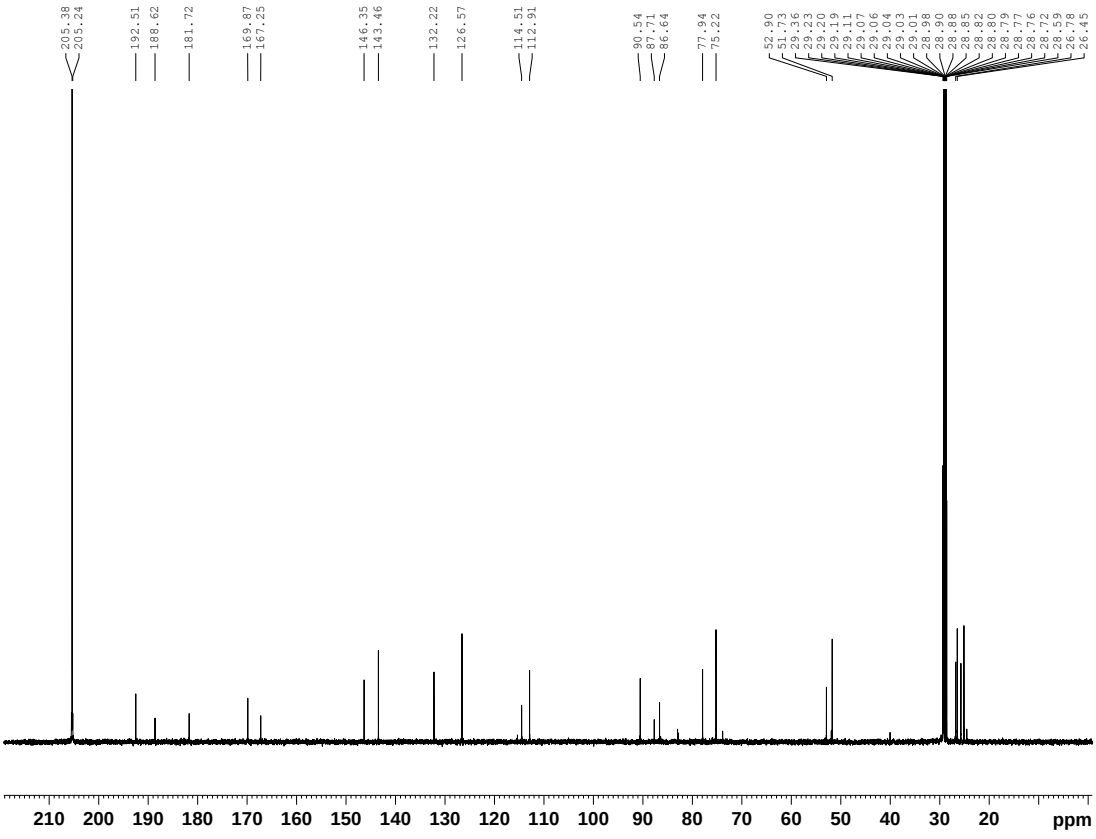
1d carbon with proton decoupling

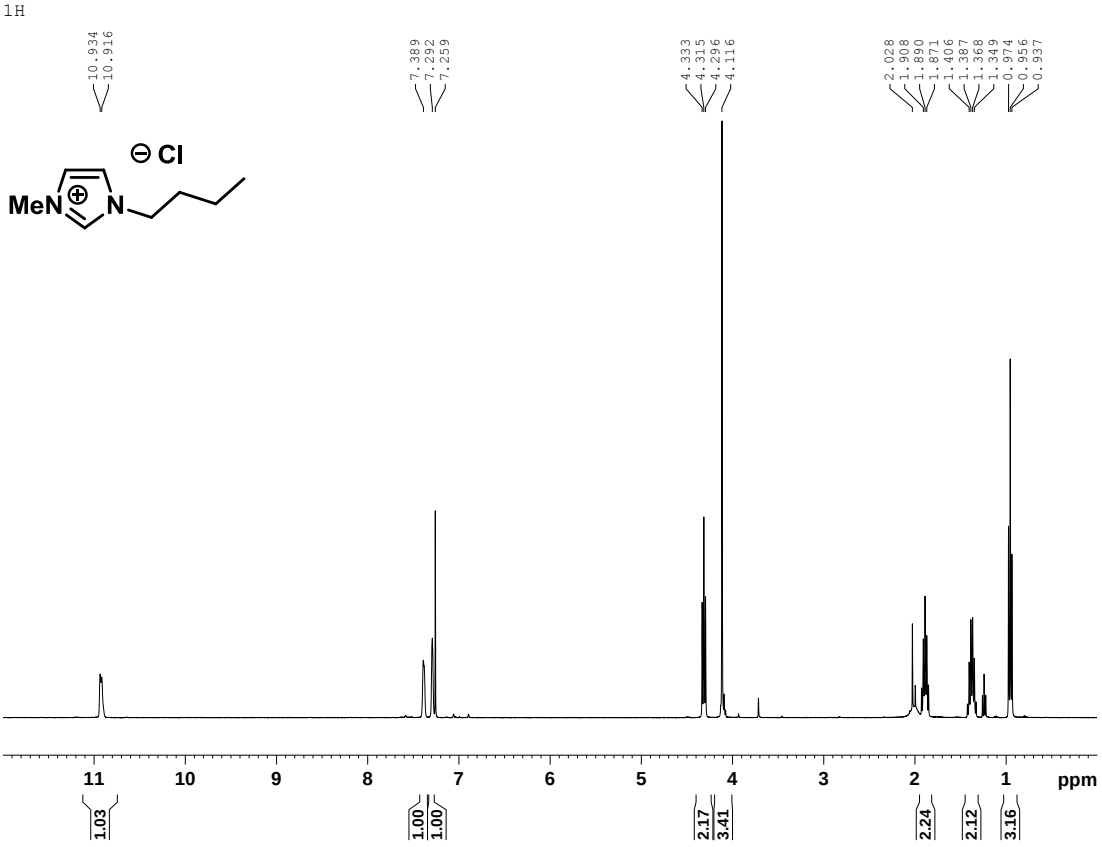


1d proton

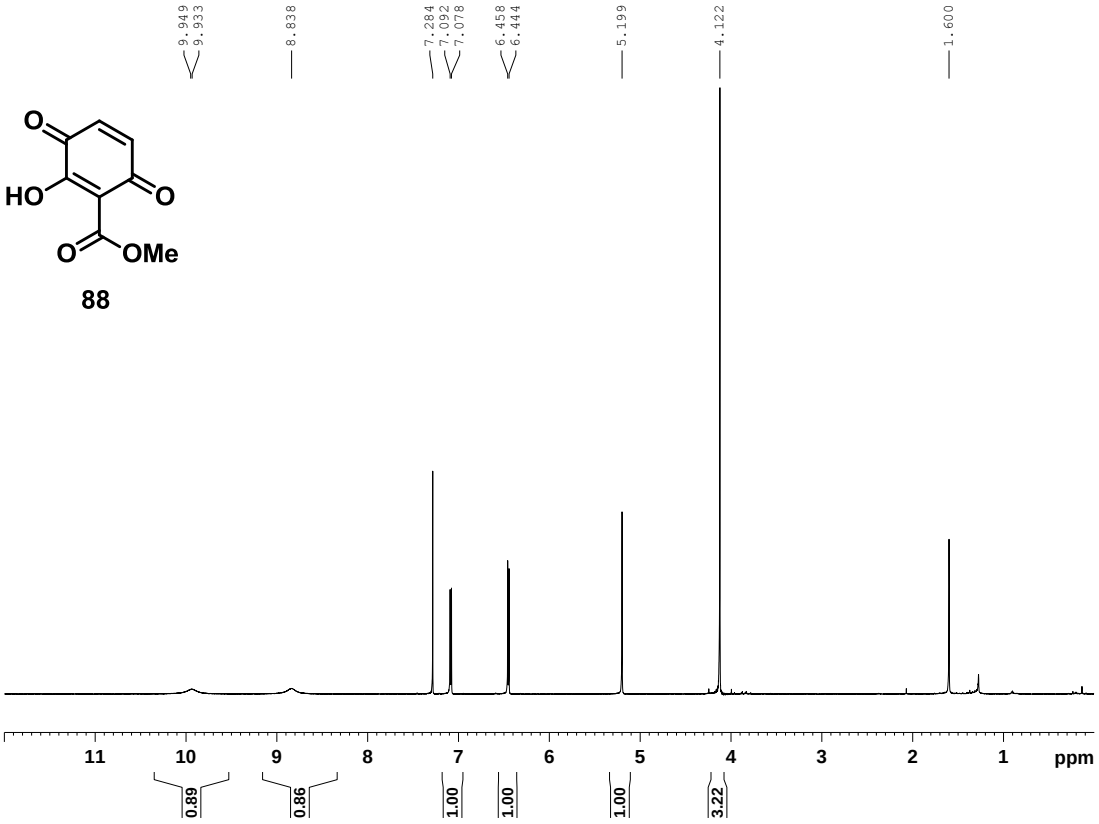



1d carbon with proton decoupling

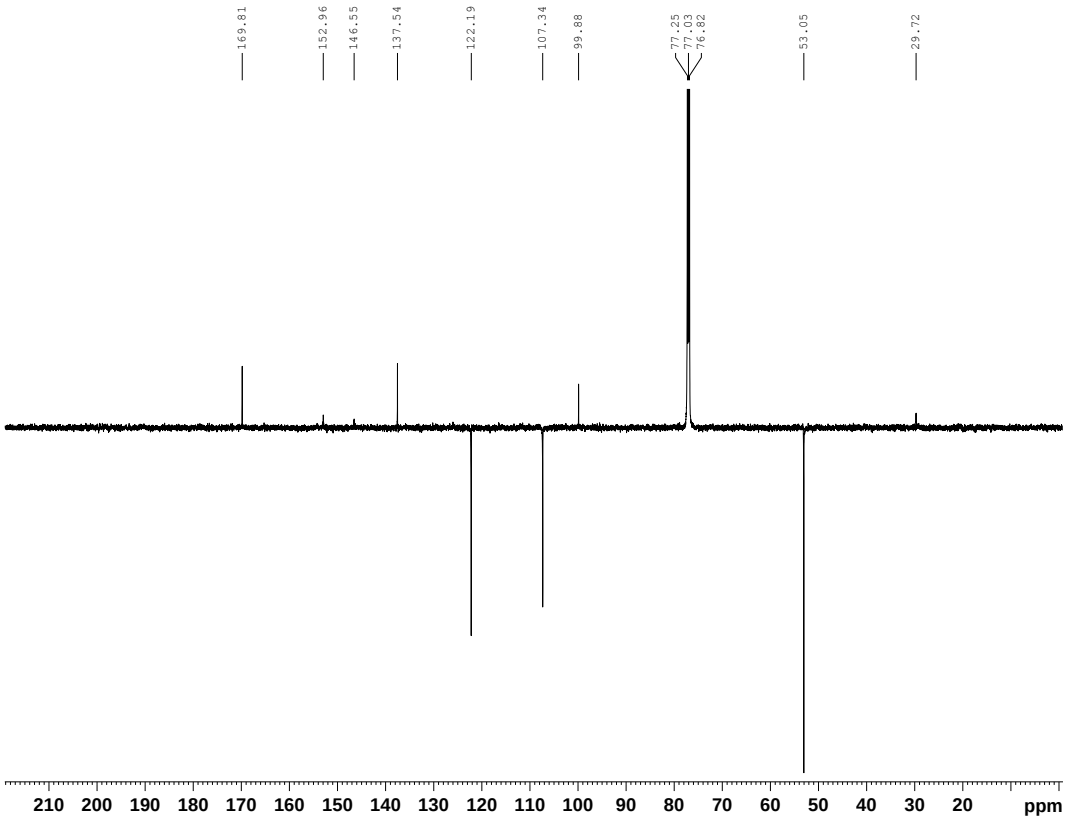



1H
10.934
10.916
7.389
7.292
7.259
4.333
4.315
4.296
4.116
2.028
1.908
1.890
1.871
1.406
1.387
1.368
1.349
0.974
0.956
0.937
⊖ Cl
MeN
N
11
10
9
8
7
6
5
4
3
2
1
ppm
1.03
1.00
1.00
2.17
3.41
2.24
2.12
3.16

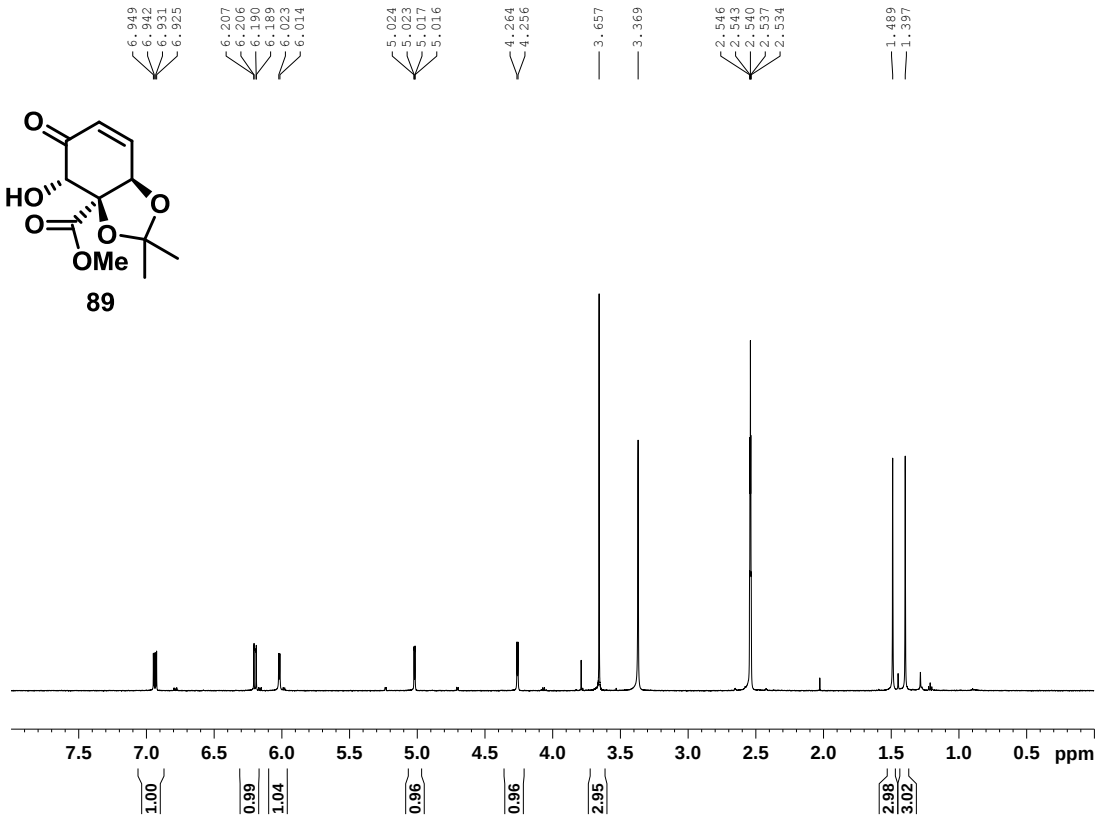
1d proton




13C DEPTQ
CH, -CH2, CH3, -Cq

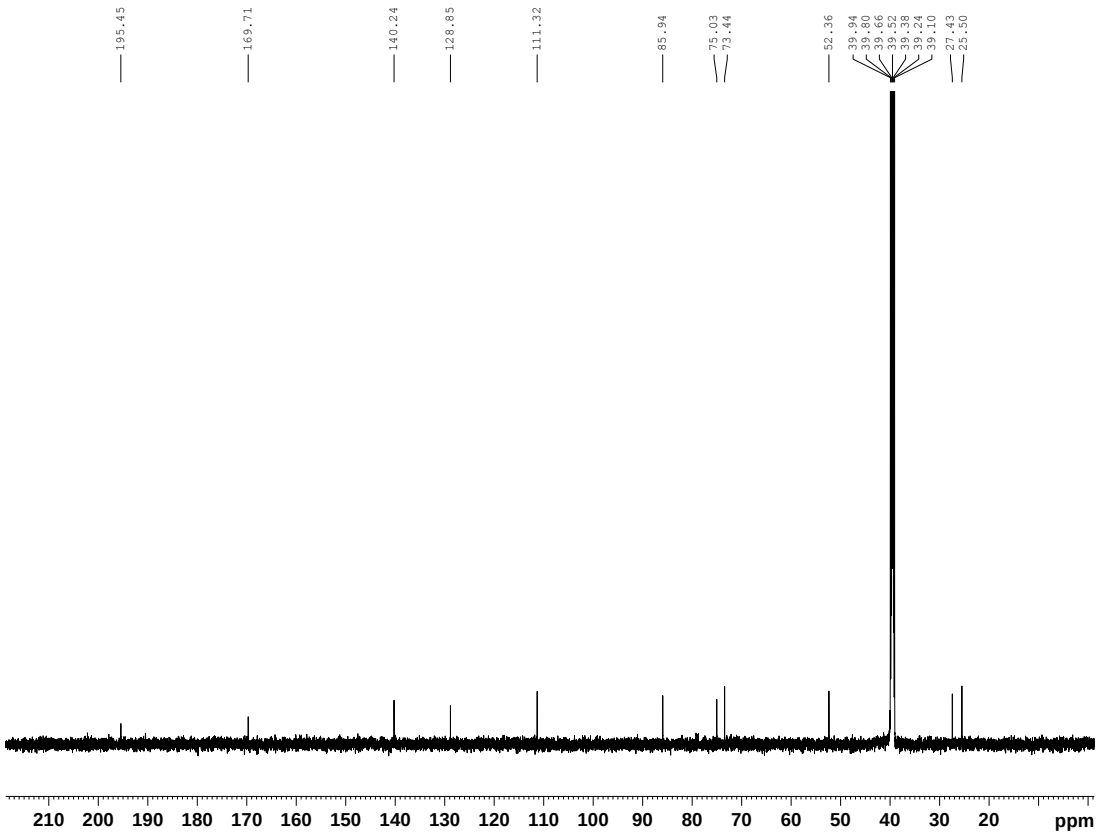


1d proton

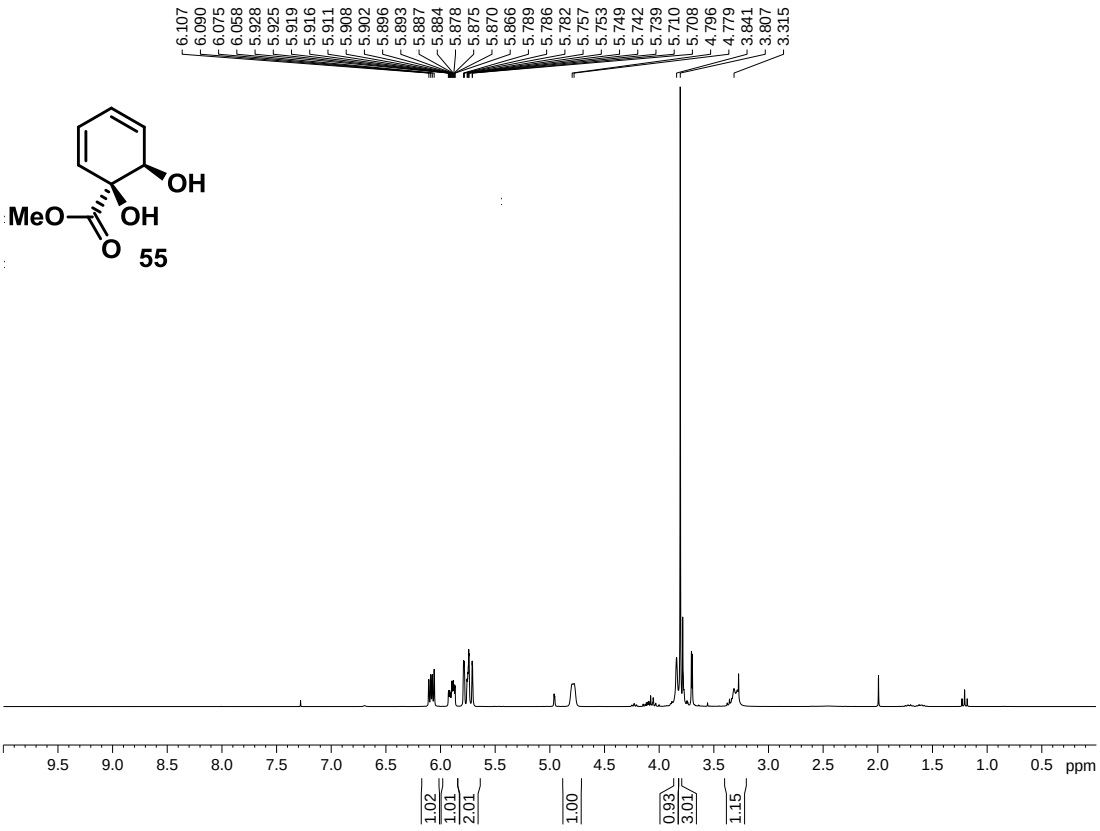



89

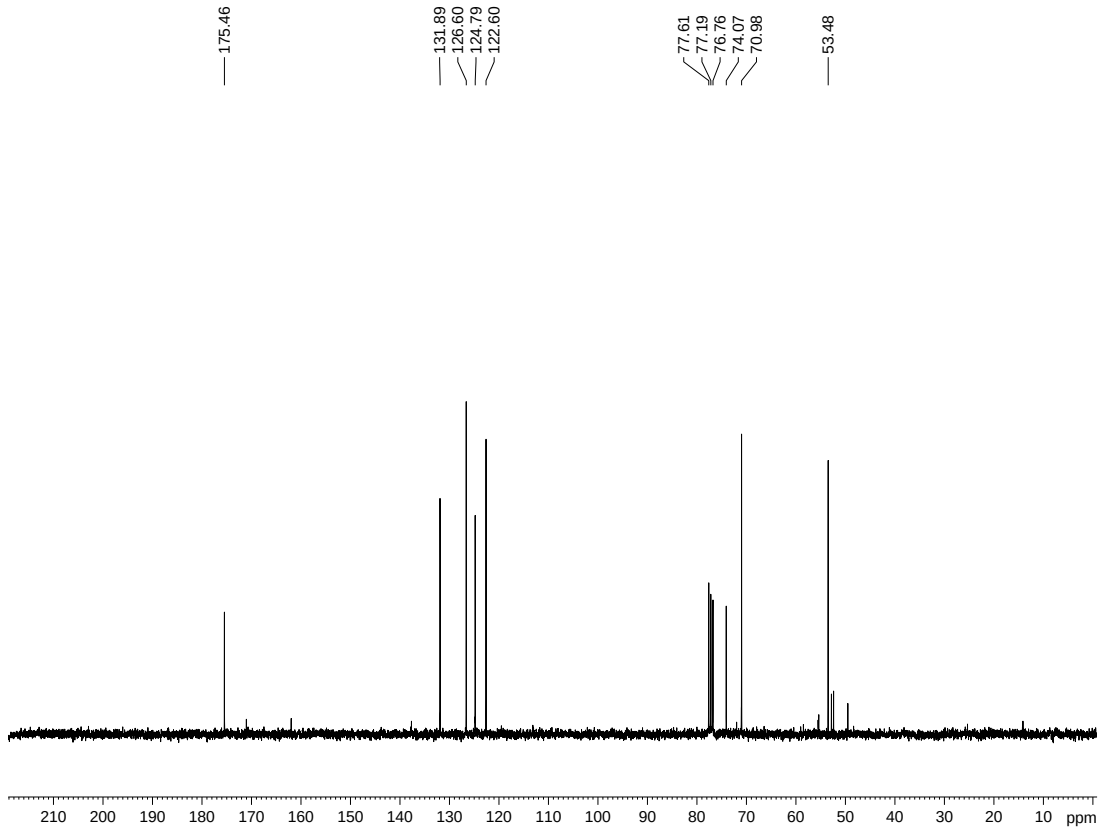
1d carbon with proton decoupling



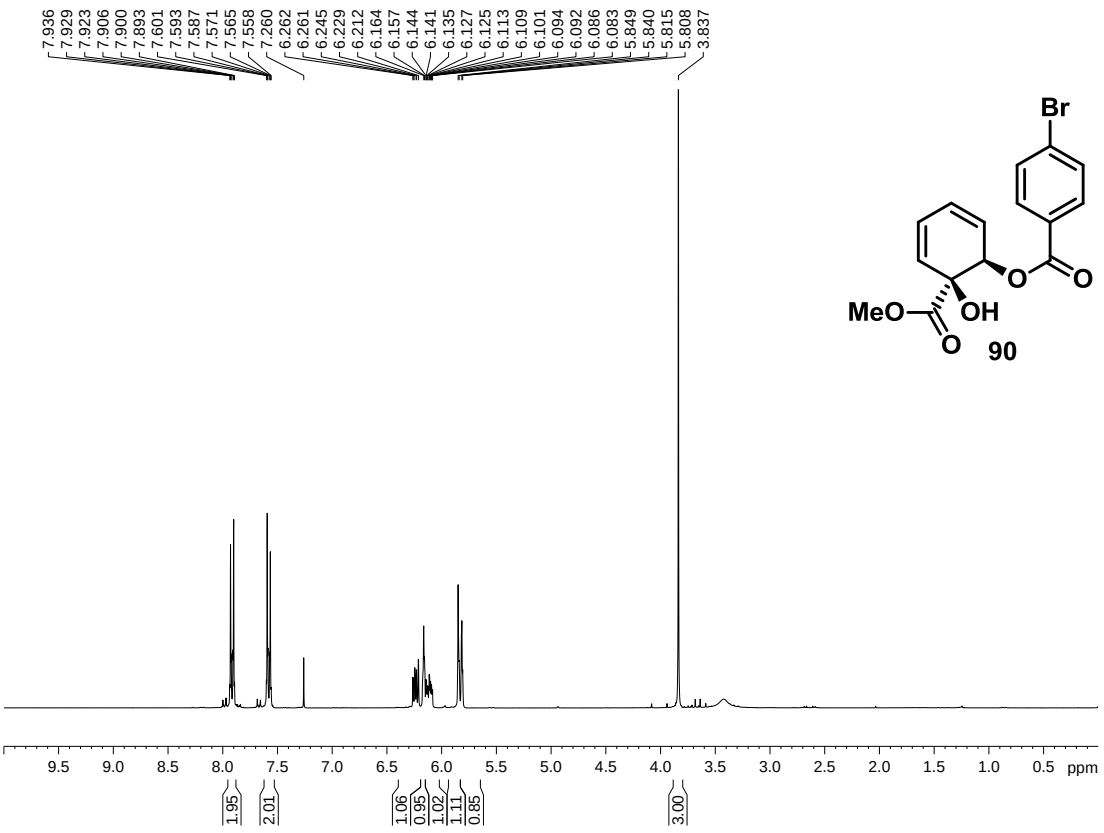
1D proton



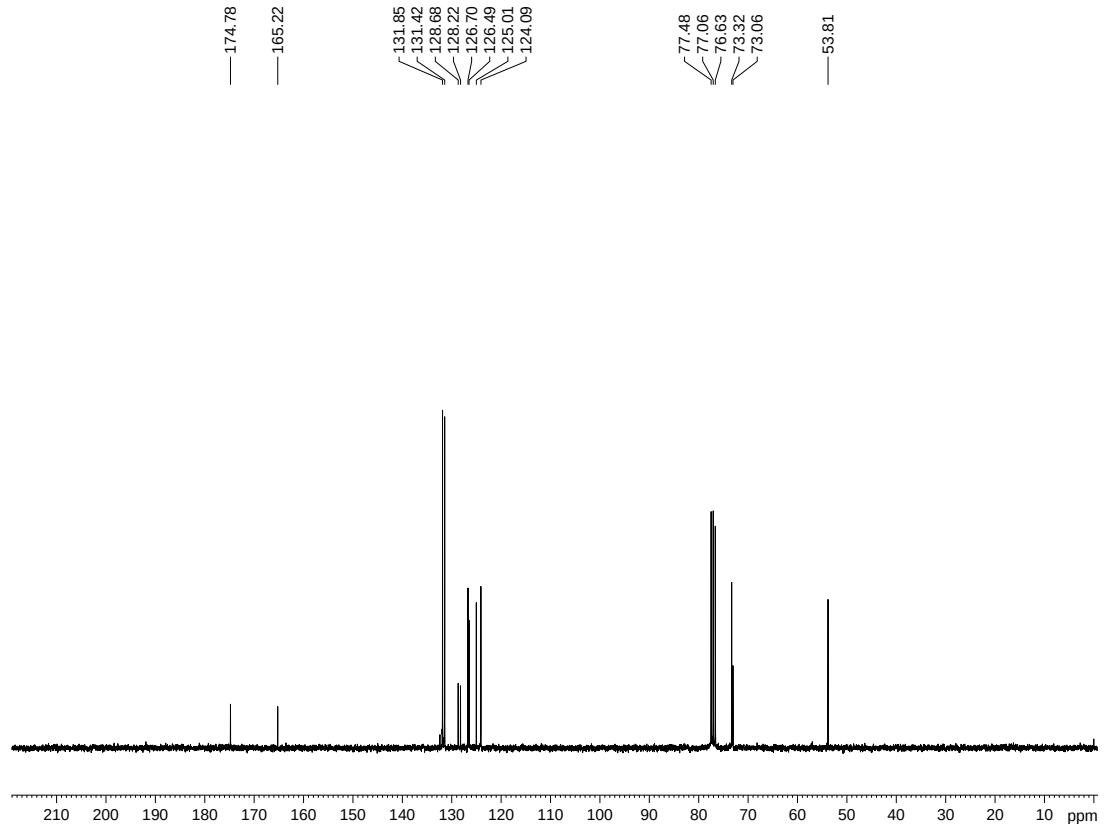

1D carbon with proton decoupling



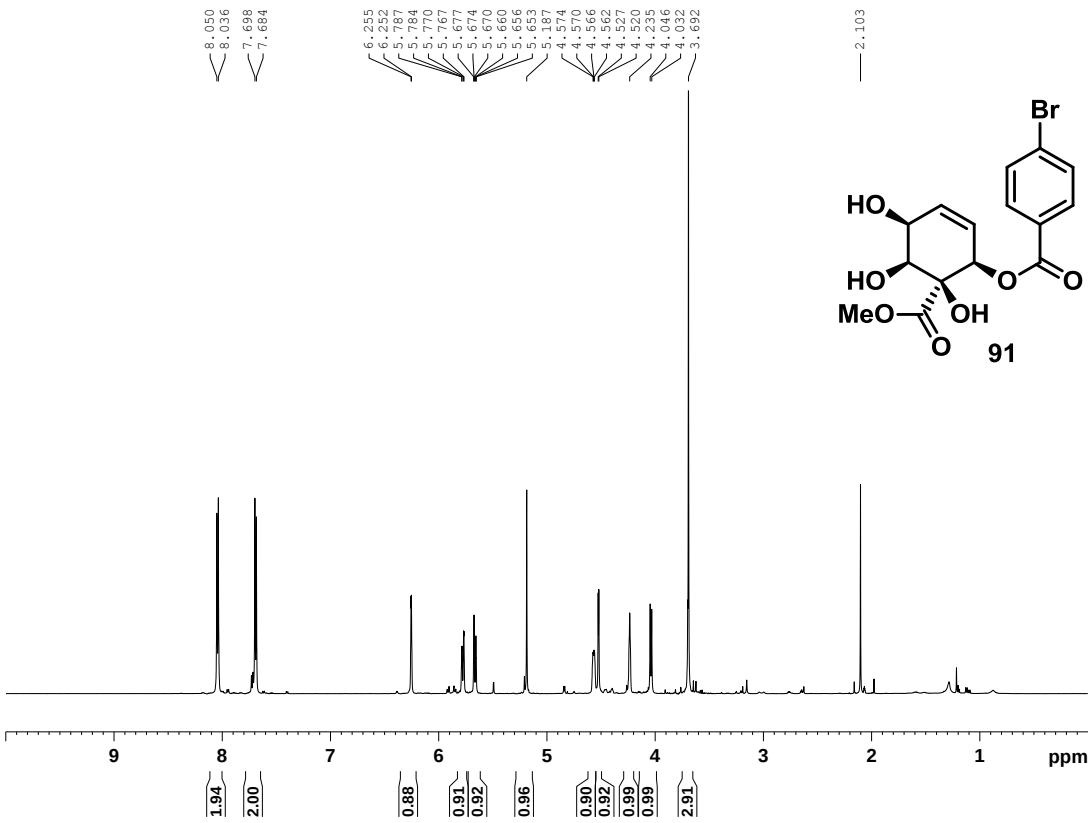
1D proton



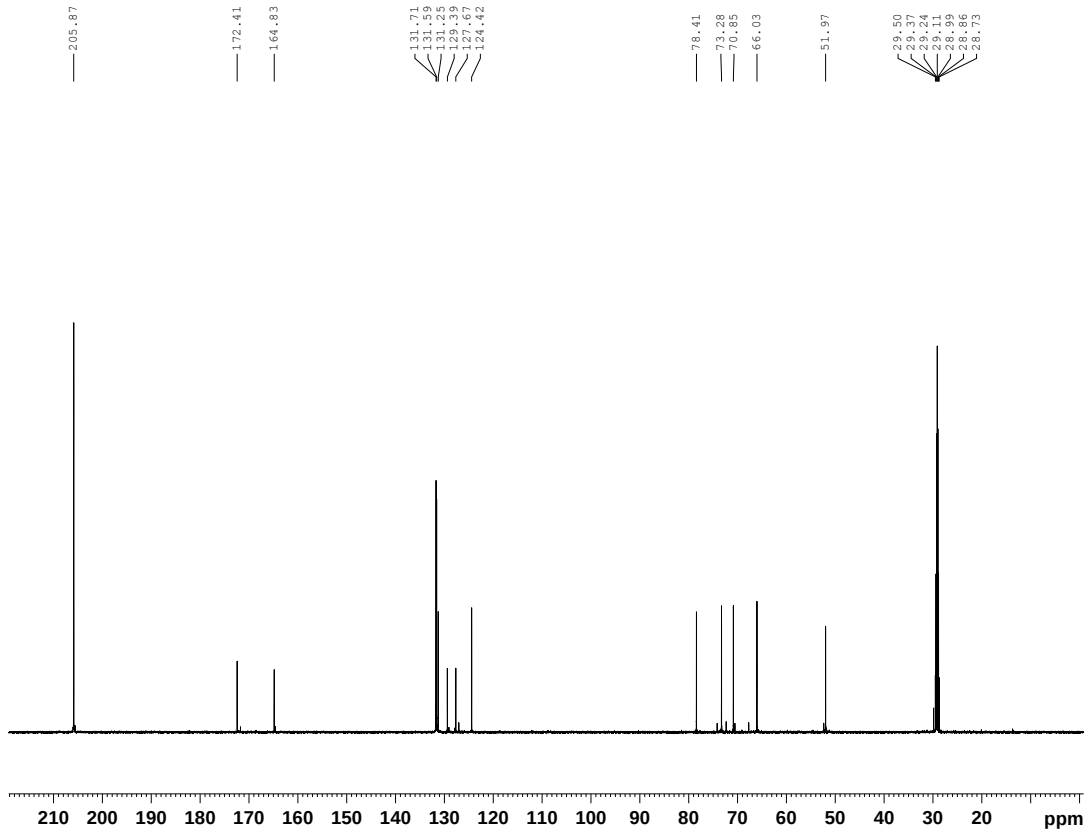

1D carbon with proton decoupling



1d proton

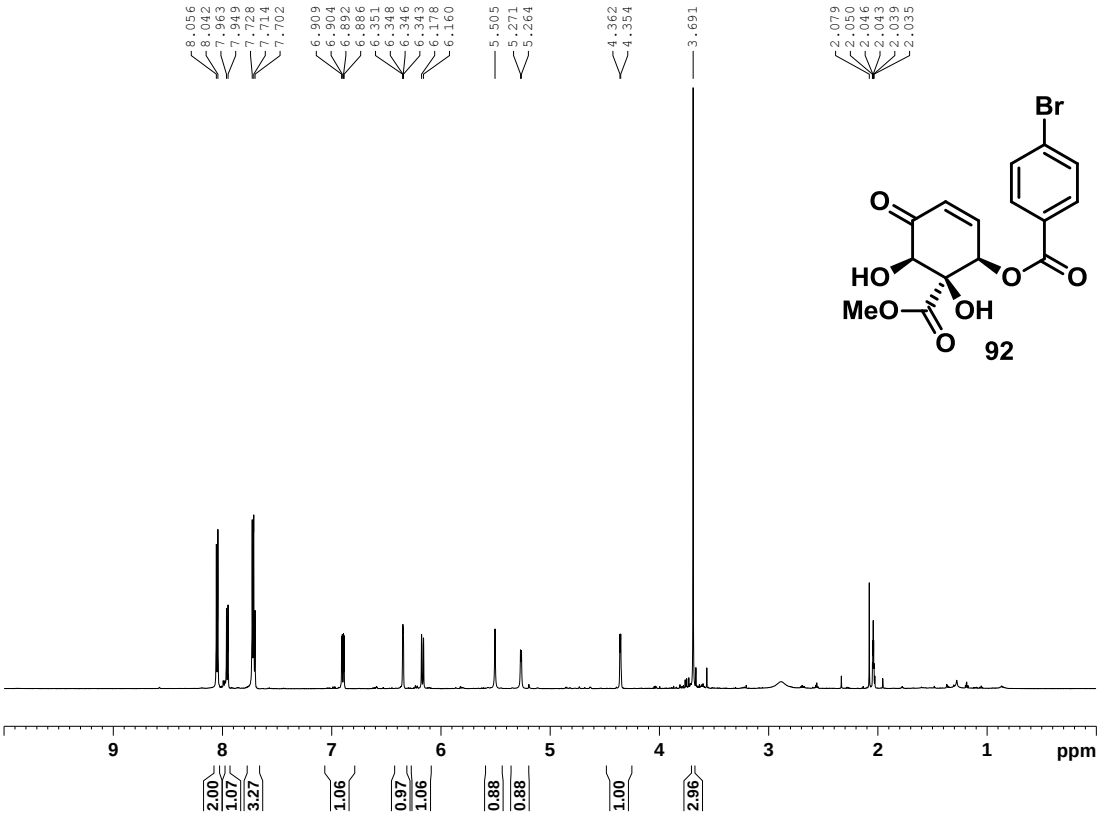



1d carbon with proton decoupling

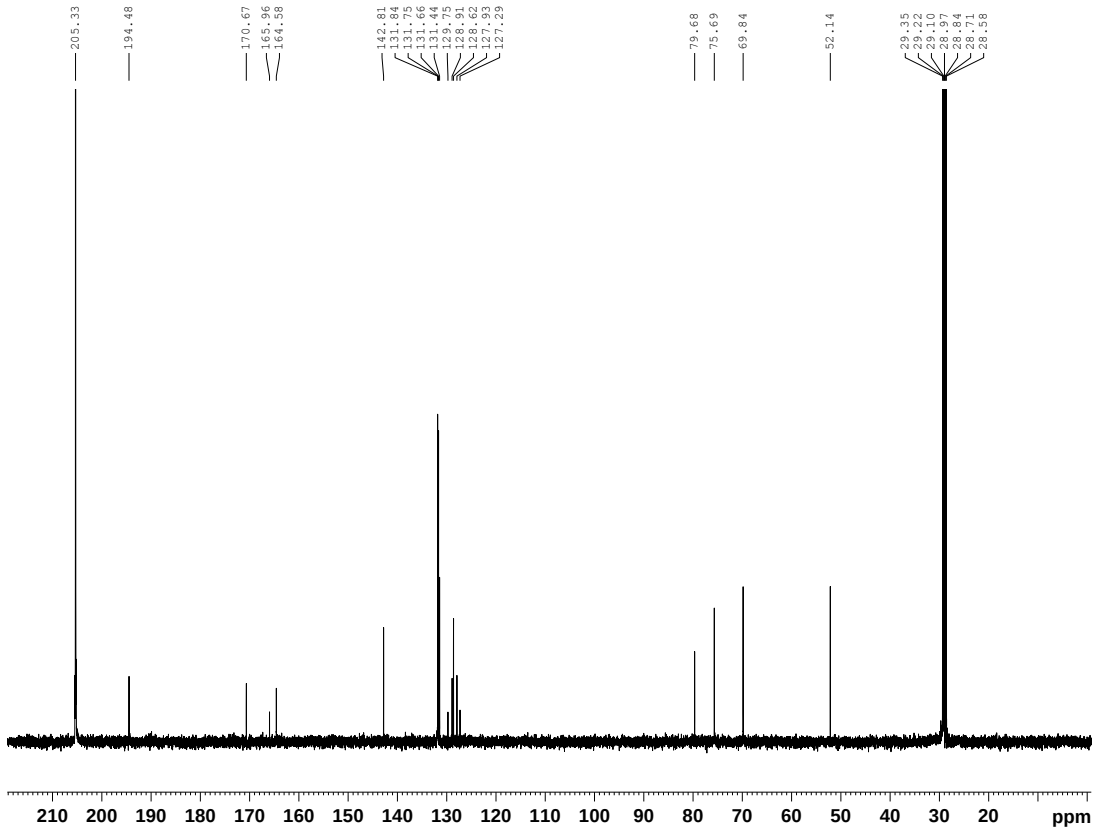



XX

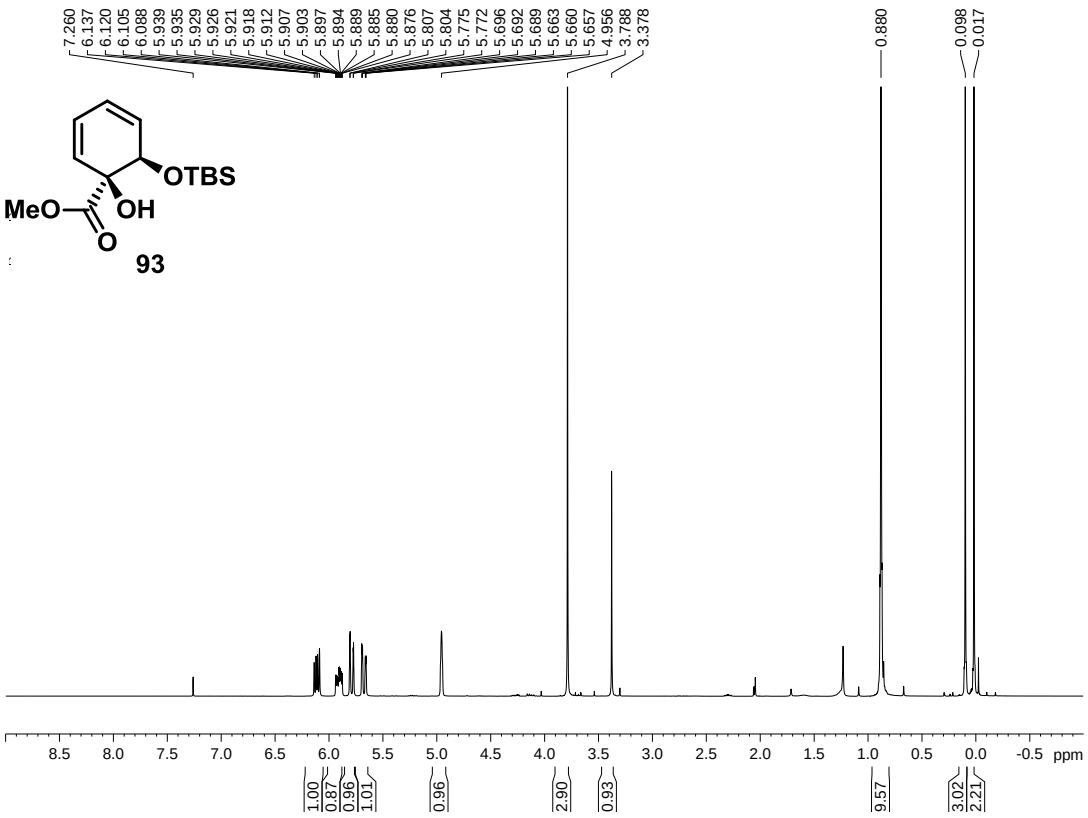
1d proton



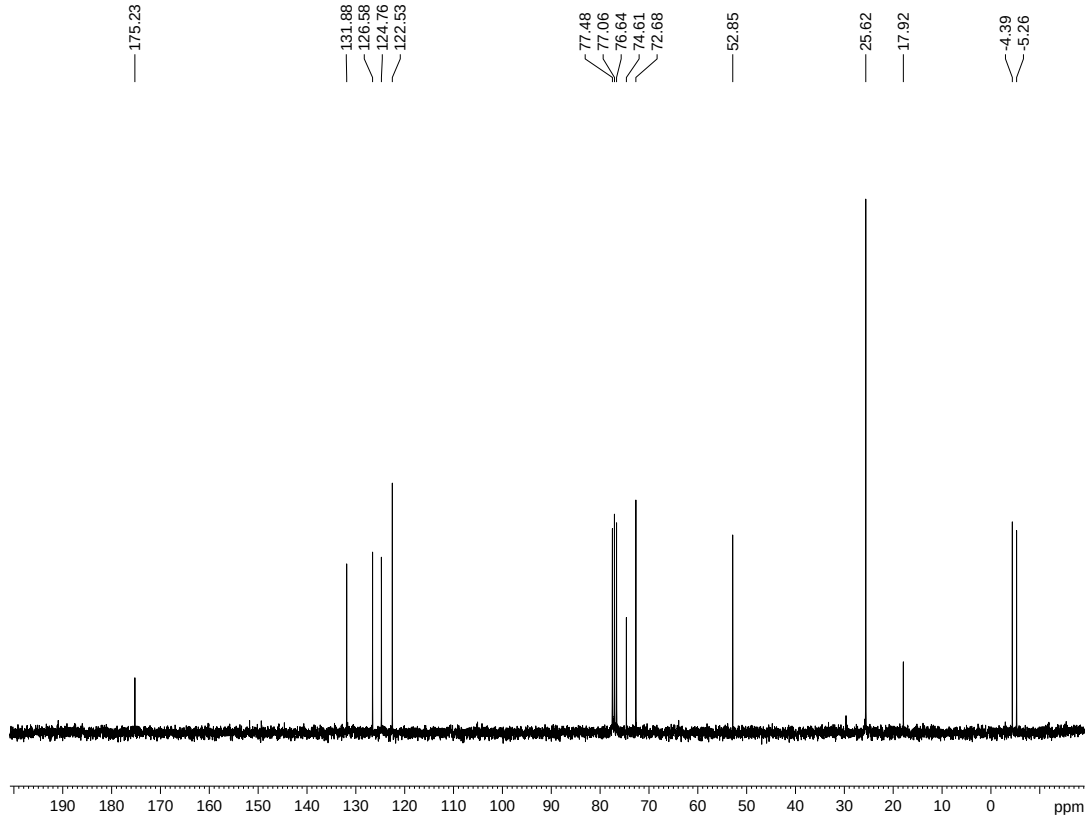

1d carbon with proton decoupling



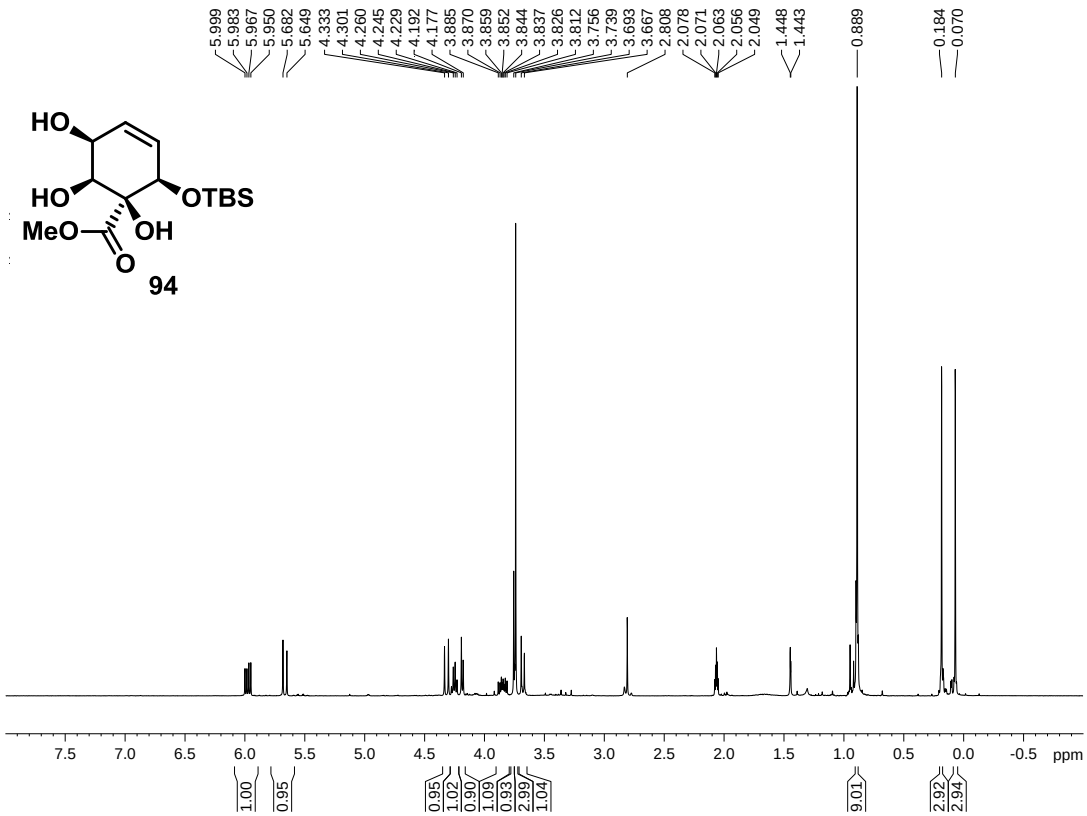
1D proton



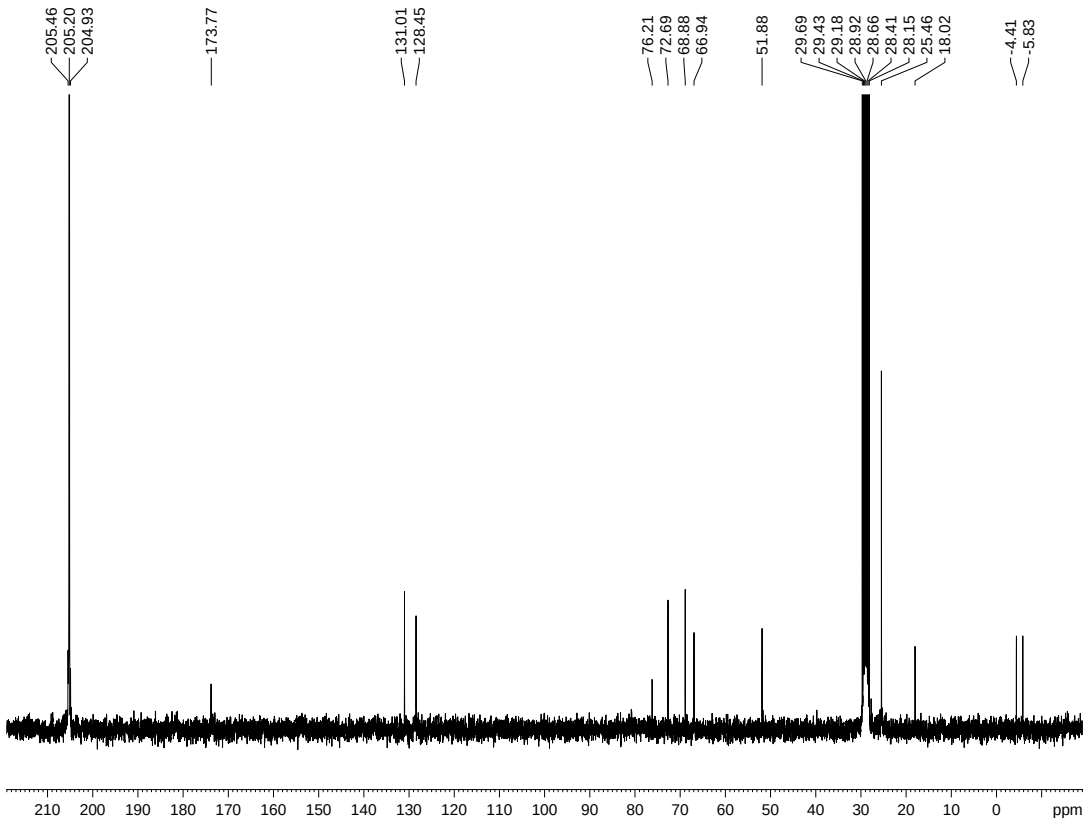

1D carbon with proton decoupling



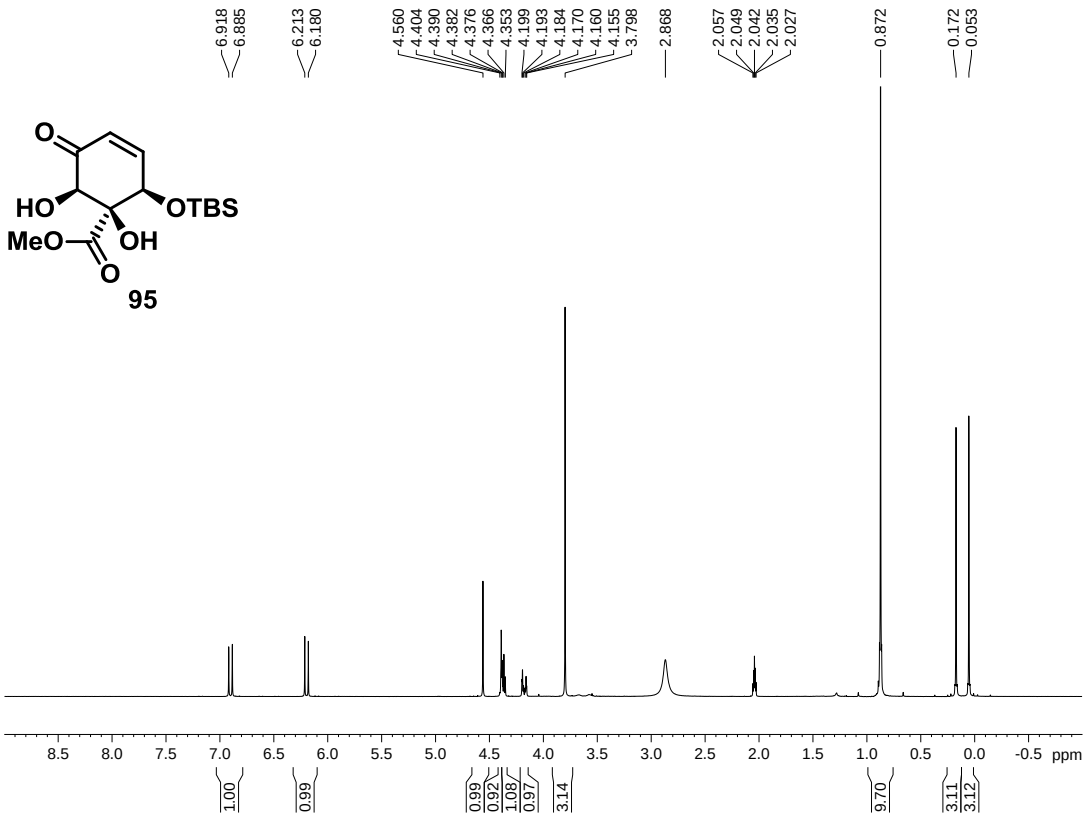
1D proton



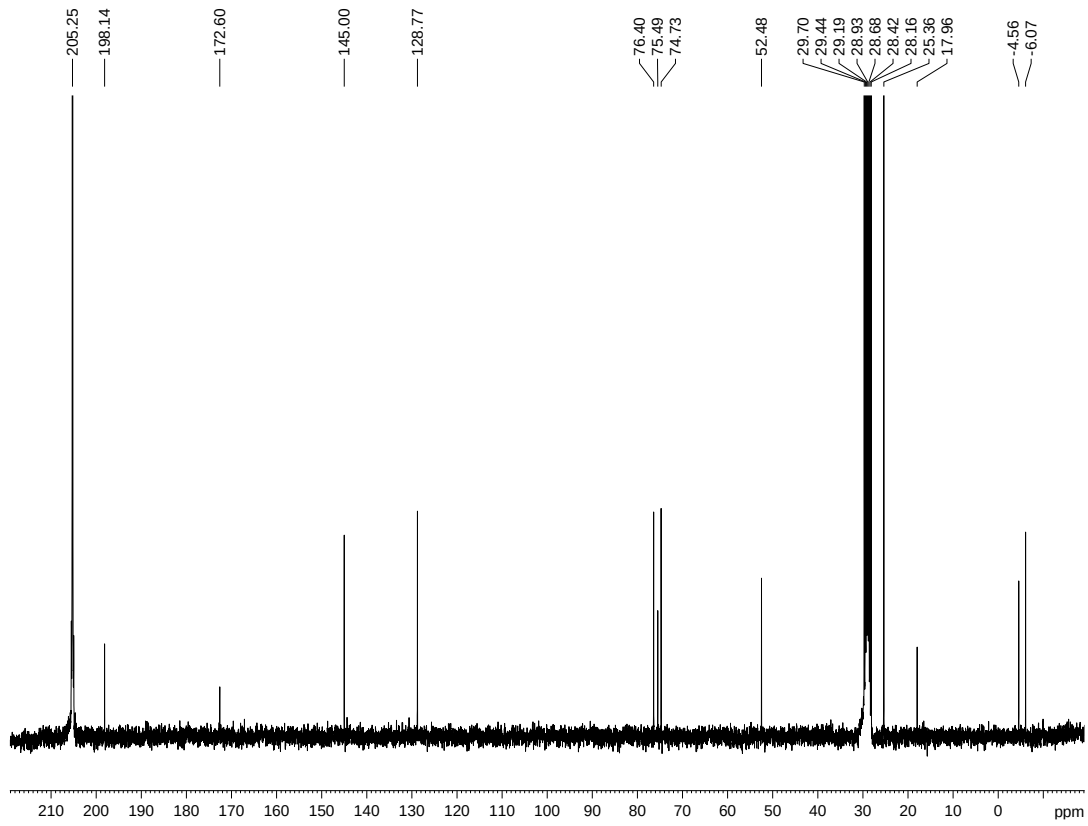

1D carbon with proton decoupling

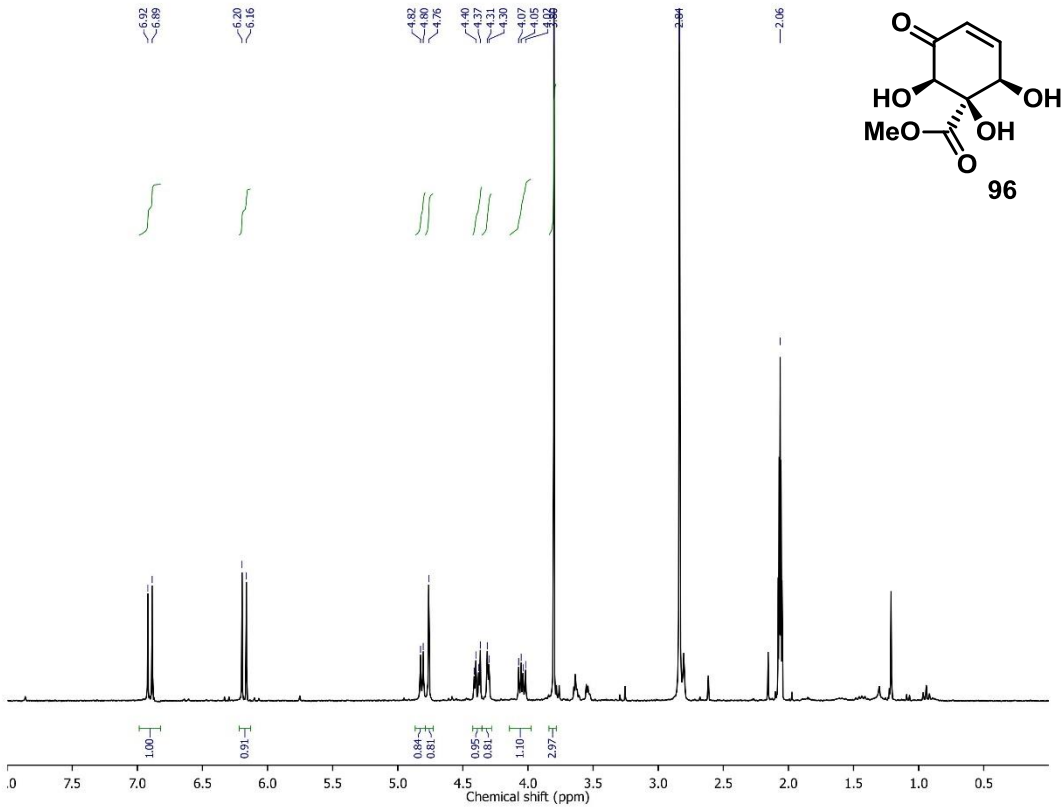


1D proton



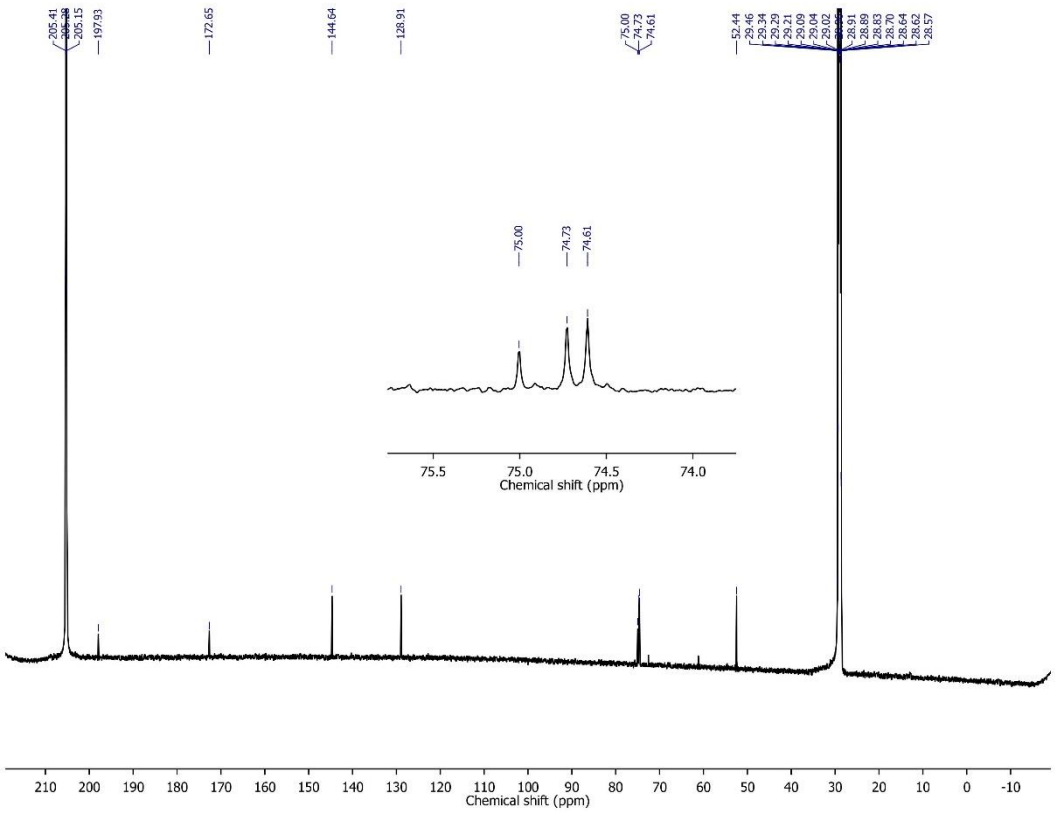

1D carbon with proton decoupling




6.92
6.89
6.20
6.16
4.82
4.80
4.76
4.40
4.37
4.31
4.30
4.07
4.05
4.02
3.94
2.06
1.00
0.91
0.84
0.81
0.95
0.81
1.10
2.97
Chemical shift (ppm)


O
HO
OH
MeO
OH
O

96


205.41
205.15
197.93
172.65
144.64
128.91
75.00
74.73
74.61
52.44
29.46
29.34
29.29
29.21
29.09
29.04
29.02
28.91
28.89
28.83
28.70
28.64
28.62
28.57
75.5
75.0
74.5
74.0
Chemical shift (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical shift (ppm)

8. Vita

Brennan A. Murphy was born in 1990 and spent much of his youth with Legos. Throughout high school and college his interest in science deepened, earning his Hon. B.Sc. Chemistry from Allegheny College in 2013 and beginning research with Dr. Hudlicky in the area of synthetic organic chemistry. His passions are in creative and practical science and technology.